AIOS TIMES

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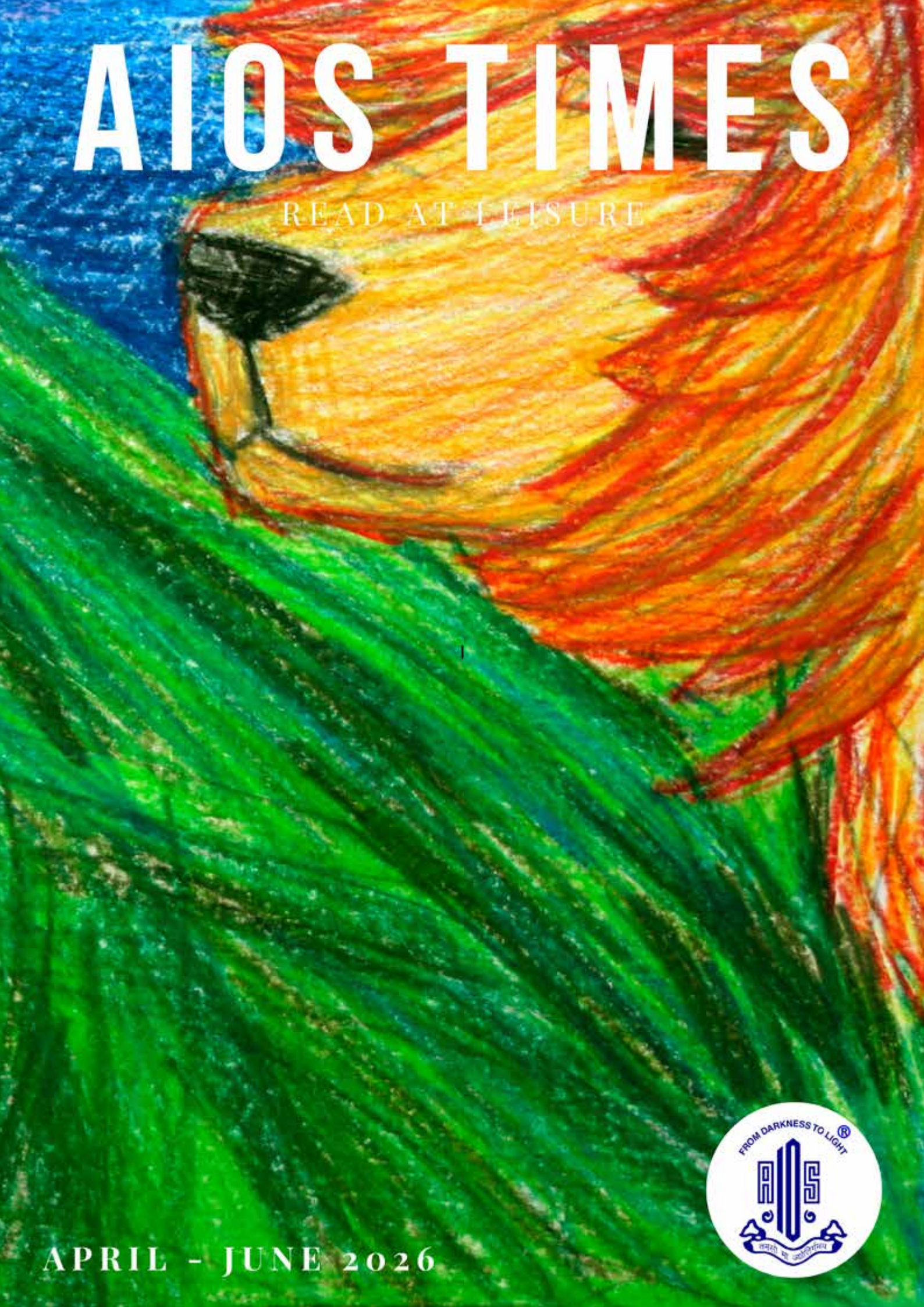
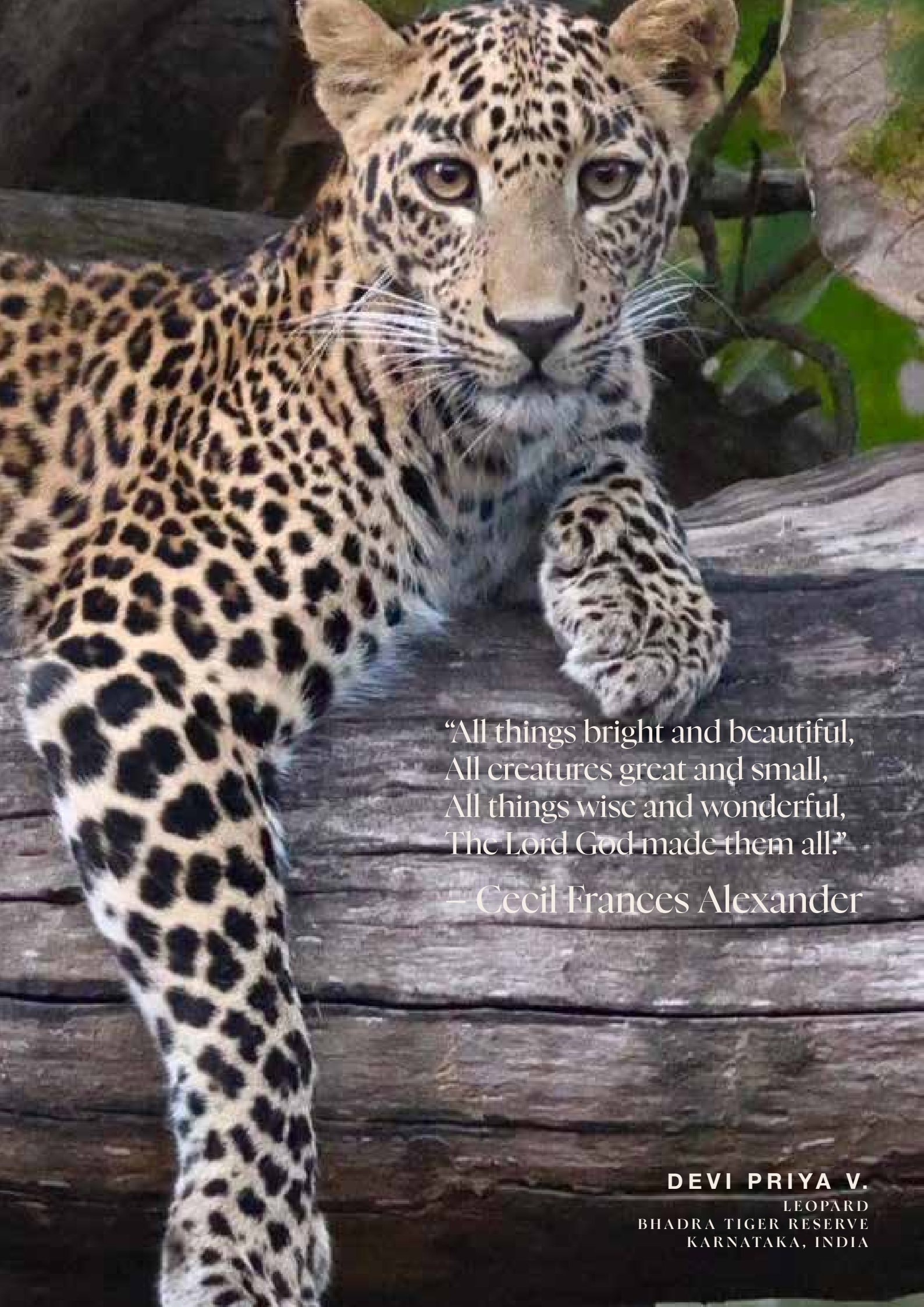


APRIL - JUNE 2026



DEVI PRIYA V.
LEOPARD
BHADRA TIGER RESERVE
KARNATAKA, INDIA

AIOS Times

Vol. 3, Issue 2 | April–June 2026

AIOS Times Editorial Board

CONTENTS

Eyedvantage

OCULAR PATHOLOGY AND MICROBIOLOGY

OCULAR ONCOLOGY

EDITORIAL

David

MRITTIKA SEN

Dr. Mrittika Sen
is an Ocular Oncologist and Ophthalmic Plastic Surgeon at Raghunath Netralaya, Mumbai. An alumnus of K.E.M Hospital, Mumbai, and Dr. R. P. Centre for Ophthalmic Sciences, AIIMS, New Delhi, she completed Fellowship in Ophthalmic Plastic Surgery and Ocular Oncology at the Centre for Sight Eye Hospital, Hyderabad, and Research Fellowship in Ocular Oncology at Wills Eye Hospital, Philadelphia, USA. Till recently, Dr. Sen was an Associate Consultant, Orbit, Oculoplasty, Reconstructive and Aesthetic Services and Ocular Oncology Services at Medical Research Foundation, Sanakara Nethralaya, Chennai. She enjoys her blog, books, absence of boredom and Bombay.

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You are hundred
And I have lived five times your age;
I was carved
But you created.

They said the marble could not be carved
Yet my master brought me to life;
You chronicled life in the deepest of oceans
And dense jungles never ventured before.

The Giant, I am a symbol of liberty
Trapped, an exhibit to flashes and eyes;
You are free, you travel at will
And capture the beauty of the wild.

My muscles taut, my stance erect
An epitome of anatomical perfection, they say;
The unfurling wings, the trembling earth beneath lithe paws
Nature through your lens is more balanced, I say.

My lips are pursed, sacred silence to Goliath's screams
Yet they read my thoughts, I know not what or why;
A mother's fear, a hungry cry, a triumphant roar, a joyful screech
You voice their tales, with humility and grace.

My eyes are alert, focused, assessing
Yet I cannot spot assailants with hammers in plain sight;
You offer a view of the best of beasts
A prey in flight, a predator in fight.

I felled Goliath
An inspiring tale of victory of the underdog;
You fall and frolic with Gorillas
Save and preserve the underdogs, you said.

You are hundred
And I have seen five times your age;
My marble mind bends to none
You mould minds to care a little more.

Man created me, a masterpiece
But man destroys;
You, mortal, are the David I wish I could be
For your savages are better than mine.

******

AIOS Times April-June 2026 Issue showcases wildlife at its best. *Eyetalics* take us on a safari into the lush forests, the animal kingdom, and the jungles of our minds. *Lenscape* features Predators, the stealthy inhabitants of the jungles who are at the top of the food chain. As the world celebrated the 100th birthday of Sir David Attenborough on May 8, 2026, the man who brought wildlife to our homes and hearts, this issue coincidentally turned out to be a fitting tribute to the legend. Volume 3 Issue 2 is also a special issue on Ocular Oncology and features an exclusive interview with Dr. Bita Esmaeli, debates, innovations and updates in the field from across the globe by Dr. Carol Shields, Dr. David Abramson, Dr. Mandeep Sagoo, Dr. Hakan Demirci and many more.

The simple lines from *The Animal Song* by Savage Garden struck a chord years ago in some of us.

"Animals and children tell the truth, they never lie
Which one is more human
There's a thought, now you decide."

As I write this Editorial today, suddenly I wonder what is in the name Savage Garden? Is it not a jungle occupied by humans to give an appearance of good and civilized, yet unable to keep up the façade any longer? Cancer is a predator, cunning, swift and powerful…the human body and the jungle have their own laws, systems, targets, and checkpoints…life and nature are both fragile…ultimately, it is all about survival. We are all Davids, fighting against Goliaths. The planet belongs to all creatures great and small. The difference is that the jungle still holds a beating heart… where have we lost ours?

Image courtesy of Shawn Meaker, via Wikimedia Commons, licensed under CC BY-SA 4.0.

APOORVA MANAGOLI

MARK 4 TIGRESS FROM JHIRNA ZONE
JIM CORBETT NATIONAL PARK
UTTARAKHAND, INDIA

EyeSee

I AM THE STEALTH, I AM THE FEAR
I AM THE SHADOW, I AM THE GOLD
I AM THE PRIDE, I AM THE POWER
THE EMPRESS OF A KINGDOM OLD.

A Conversation with the Legends.

SHOBHIT CHAWLA
TIGRESS
PILIBHIT TIGER RESERVE
UTTAR PRADESH, INDIA

I N C O N V E R S A T I O N

with **Dr. Bita Esmaeli**

Dr. Kirthi Koka
is a Senior Consultant and Deputy Director of the Orbit, Oculoplasty, Reconstructive and Aesthetic Services at Sankara Nethralaya, Chennai. She completed her MBBS from Kilpauk Medical College and Hospital, Chennai and Ophthalmology residency from Stanley Medical College, Chennai. She completed her Fellowship in Orbit and Oculoplasty from Sankara Nethralaya, Chennai. Her areas of interest include orbit and adnexal oncology, eyelid surgeries and thyroid eye disease. She has presented at various national and international conferences and has published her work in peer reviewed journals.

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Building a Legacy

Through Challenge, Innovation, and Compassion

Dr. Bita Esmaeli is an internationally acclaimed ophthalmic oncologist, orbital surgeon, and pioneer in ocular adnexal cancer care. She served as a tenured Professor of Ophthalmology at The University of Texas MD Anderson Cancer Center, Houston, from 1998 to 2024, where she founded and led the Section of Ophthalmology and directed the Ophthalmic Plastic Surgery Fellowship Program for over two decades. She currently holds academic appointments at the University of Houston Fertitta College of Medicine and at the Houston Methodist Hospital Academic Institute/Weill Cornell Medical College Department of Ophthalmology (bitaesmaeli.com).

Widely recognized for advancing the field of orbital and adnexal oncology, Dr. Esmaeli has championed vision- and eye-preserving treatments for lacrimal gland and orbital cancers, pioneered the application of sentinel lymph node biopsy in periocular malignancies, and contributed significantly to the development of modern ophthalmic oncology staging systems. Her research focuses on improving cancer outcomes while preserving vision and quality of life.

With more than 340 peer-reviewed publications, numerous clinical trials, and leadership roles including co-chair of the AJCC Ophthalmic Oncology Task Force and the TCGA Uveal Melanoma Project, Dr. Esmaeli has shaped contemporary ophthalmic oncology worldwide. Her many honors include the ASOPRS Wendell Hughes Lecture Award in 2022, AAO Lifetime Achievement Award (2025), Merrill Reeh Pathology Award, the Research Award from the American Society of Ophthalmic Plastic and Reconstructive

While institutions often separate clinicians and scientists into different tracks, I believe the most impactful translational research happens when clinicians work closely with basic scientists.

Surgery (ASOPRS), and multiple national awards for research, education, and clinical excellence.

From her early years in Iran to establishing one of the world's leading ophthalmic oncology programs, her journey is a testament to resilience, innovation, and an unwavering commitment to patient care. In this conversation, she reflects on the experiences that shaped her career and shares valuable lessons for the next generation of ophthalmologists.

KK: Could you tell us about some of the experiences that shaped your journey in medicine?

BE: My earliest inspiration came from my parents, both physicians. My father was a general surgeon and my mother an obstetrician-gynecologist. I especially remember accompanying my father to his practice in an underserved area of Tehran. Watching him care for patients from all walks of life left a deep impression on me. I realized very early that I wanted to become a physician.

More recently, my father passed away at the age of 94. Reflecting on his life reminds me how much he influenced my professional values. His dedication to service and his compassion toward patients remain my greatest inspirations.

KK: You completed a Master's degree in Cell Biology and Physiology before medical school. What led you down that path?

BE: Interestingly, it was not part of a grand plan. After completing college in the United States, geopolitical tensions between Iran and the United States created visa challenges that delayed my ability to apply to medical school. Rather than abandoning my dream, I pursued a Master's degree while waiting for my immigration status to be resolved.

Looking back, that period was invaluable. It gave me a deeper appreciation of basic science and research. More importantly, it taught me a lesson that has stayed with me throughout my life: many circumstances are beyond our control, but we can always make the best of what we are given.

KK: Did your scientific training influence the way you approach tumor biology and ocular oncology today?

BE: Absolutely. It helped me appreciate how discoveries are made and how much effort is required to translate basic science into meaningful advances in patient care. I strongly believe that some of the most important medical breakthroughs occur at the intersection of clinical medicine and laboratory science.

While institutions often separate clinicians and scientists into different tracks, I believe the most impactful translational research happens when clinicians work closely with basic scientists. Clinicians understand the real-world problems patients face, and that perspective is critical in asking the right research questions.

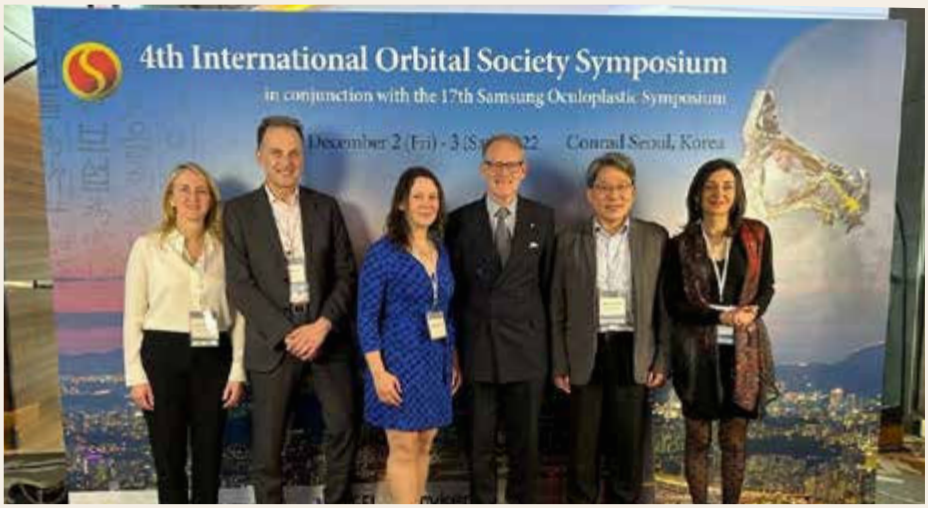
KK: What drew you toward ophthalmology and eventually oculoplastic surgery?

BE: During medical school, I genuinely enjoyed every specialty. However, I knew I was a surgeon at heart. I enjoy solving problems, making decisions, and seeing tangible results.

Originally, I considered general surgery because my father was a surgeon. However, the culture of surgical training at the time was extremely difficult, particularly for women. My experiences during surgical rotations convinced me that general surgery was not the right environment for me.

That led me to explore other surgical specialties, and ophthalmology stood out.

Within ophthalmology, I was eventually drawn to oculoplastics because of its creativity and diversity. Every case is different. It requires both technical skill and thoughtful problem-solving, which suited my personality.



Dr. Esmaeli with colleagues at the Orbital Society meeting in Seoul, South Korea

It was intellectually challenging, highly competitive, and offered extraordinary opportunities to combine medicine and surgery.

Within ophthalmology, I was eventually drawn to oculoplastics because of its creativity and diversity. Every case is different. It requires both technical skill and thoughtful problem-solving, which suited my personality.

KK: How did you transition from oculoplastics into oncology?

BE: That transition happened largely because of circumstances. After fellowship, my husband's career brought us to MD Anderson Cancer Center. At the time, there was no established ophthalmology department there. I entered what seemed like a very uncertain situation.

What initially appeared to be a risk turned out to be an extraordinary opportunity. I found myself in an environment filled with complex cancer patients and multidisciplinary expertise. Over time, I helped develop what is now recognized as oncologic ophthalmic plastic surgery and orbital oncology.

One recurring theme in my life is that challenges often become opportunities. Many of the defining moments in my career emerged from situations that initially appeared difficult or even undesirable.

At the International Society of Ocular Oncology Conference held at Goa in 2024

At the Pan American Ocular Oncology Symposium in Monterrey, Mexico

KK: Which mentors had the greatest influence on your development as a surgeon?

BE: My residency at the University of Michigan provided an incredibly strong foundation. The expectation was that residents would arrive fully prepared and take ownership of their education. Although it was demanding, it produced well-rounded ophthalmologists capable of managing a wide range of problems.

My fellowship mentors in Toronto also shaped my surgical philosophy. They emphasized efficiency, decisiveness, and practical problem-solving. One of the most important lessons I learned was to focus on accomplishing the surgical objective effectively rather than becoming lost in unnecessary details.

The second lesson was the importance of remaining calm and adaptable when unexpected challenges arise in the operating room. Those principles continue to guide my practice today.

KK: Working with cancer patients can be emotionally demanding. How did you navigate that early in your career?

BE: It was profoundly moving. During my first year at MD Anderson, I spent a great deal of time caring for very ill patients, many of whom were nearing the end of life. Those experiences affected me deeply.

Yet I also discovered something important: cancer patients give as much as they receive. Caring for them provides a sense of purpose and perspective. Their courage, resilience, and humanity are incredibly inspiring.

Over time, I learned the importance of balancing empathy with professional distance. Patients need compassion, but they also need clear judgment and confident guidance. As physicians, we must remain emotionally present while still making the best decisions for their care.

Yet I also discovered something important: cancer patients give as much as they receive. Caring for them provides a sense of purpose and perspective. Their courage, resilience, and humanity are incredibly inspiring.

Dr. Esmaeli with a pediatric oncology patient

Innovation often requires the willingness to explore paths that others may not initially support.

KK: What gave you the confidence to build an entire ophthalmic oncology service?

BE: I think much of it stems from my early life experiences. At age fifteen, I moved from Iran to the United States and attended boarding school. I had to adapt to a new language, culture, and environment without my immediate family.

Those experiences fostered independence and resilience. Later, when opportunities or challenges arose, I was comfortable stepping into unfamiliar territory.

I have always been inclined to think independently and question conventional approaches. Sometimes that means challenging established practices. Innovation often requires the willingness to explore paths that others may not initially support.

KK: Can you share an example of that mindset?

BE: One example is our work on lacrimal gland adenoid cystic carcinoma. Historically, many patients underwent orbital exenteration because of concerns about delivering radiation near the eye.

I questioned whether that approach was always necessary. Working with multidisciplinary colleagues, we explored eye-preserving strategies that could maintain both oncologic control and quality of life. That required challenging established assumptions, but it ultimately opened new possibilities for patients.

Dr. Esmaeli at the Karolinska Institutet, Sweden

KK: What were the biggest challenges in establishing a dedicated ophthalmic oncology service at MD Anderson?

BE: One challenge was helping others appreciate the importance of the field. Orbital and adnexal tumors are rare, and they cannot compete with major cancers in terms of patient volume. However, they present unique clinical challenges and opportunities.

Orbital and adnexal tumors are rare, and they cannot compete with major cancers in terms of patient volume. However, they present unique clinical challenges and opportunities.

We had to demonstrate that preserving vision, maintaining appearance, and achieving excellent cancer outcomes were all worthwhile goals. Building support required communicating that vision effectively and showing the value of investing resources into the specialty.

Like any large institution, there were also organizational and political challenges. But I remained focused on advancing the field through patient care, research, and education.

KK: You pioneered several innovations, including sentinel lymph node biopsy for periocular tumors and eye-preserving treatments for lacrimal gland cancers. How did those ideas develop?

BE: Many innovations emerge from curiosity and multidisciplinary collaboration. The idea of sentinel lymph node biopsy came after attending a conference where surgeons were discussing its use in head and neck cancers. I immediately wondered why the same principles could not be applied to periocular tumors.

That simple question led to clinical trials, research, and eventually broader adoption of the technique.

I believe innovation often begins when you focus deeply on a specific niche area and remain curious. The most rewarding discoveries frequently arise from asking questions that others have not yet explored.

KK: You have participated in several leadership development programs. Would you encourage young ophthalmologists to pursue formal leadership training?

BE: Absolutely. Leadership training should not be reserved only for those who aspire to administrative positions. Every physician is a leader. We lead our operating rooms, our clinical teams, our trainees, and often our patients through difficult decisions.

Leadership training should not be reserved only for those who aspire to administrative positions. Every physician is a leader. We lead our operating rooms, our clinical teams, our trainees, and often our patients through difficult decisions.

Dr. Bita Esmaeli with colleagues at the American Academy of Ophthalmology Meeting at Chicago in 2022 where she was conferred the prestigious Wendell L. Hughes Lecture Award

My advice is to pursue what genuinely excites you. There is no single definition of success. The important thing is to make choices that align with your values and priorities.

For physicians working within large hospitals or academic institutions, leadership programs offer additional benefits. They provide insight into organizational culture, help build meaningful professional relationships, and improve communication and decision-making skills.

Healthcare systems have become increasingly complex. Modern leadership requires competencies that extend beyond clinical excellence. Financial literacy, administrative understanding, strategic thinking, and organizational management are becoming increasingly important.

Not every physician needs to become a department chair or hospital executive, but leadership skills benefit everyone. For those who have both the talent and the interest to pursue larger leadership roles, formal training can be an invaluable investment in their future.

KK: What advice would you give young women pursuing careers in ophthalmology and academic medicine?

BE: Every generation faces different challenges. When I was training, women often carried the majority of family responsibilities while building demanding careers. Today, there is greater support, more flexibility, and increasing participation from partners in parenting.

My advice is to pursue what genuinely excites you. There is no single definition of success. Some people find fulfillment primarily through patient care, others through research, education, leadership, or a combination of these.

Work-life balance is an ongoing challenge, and there are always trade-offs. I am immensely proud of my professional accomplishments, but I am equally proud of being a mother. The important thing is to make choices that align with your values and priorities.

With colleagues, Dr. Claire Daniel and Dr. Michele Beaconsfield at the Adnexal Oncology Service at Moorfields, NHS, London

In today's world, information is everywhere. Artificial intelligence and digital tools can generate knowledge rapidly. What will distinguish physicians is not simply information, but our humanity—our experience, compassion, judgment, and ability to connect with patients. Those qualities are irreplaceable, and they are what I hope every fellow carries forward.

KK: Burnout has become a major concern among trainees and young ophthalmologists. What advice would you offer on balancing professional curiosity with personal well-being?

BE: This is a very important issue, and I must admit that I did not always get the balance right myself. For much of my career, my life revolved around two priorities: my work and my son. It was not until my son left for college, when I was around fifty years old, that I consciously allowed myself to pursue interests outside medicine.

Over the last decade, I have become a much more balanced person. I joined a church choir, where I sing soprano, and I began taking painting classes. Initially, painting appealed to me because the creative process was completely different from my daily work. Medicine and surgery require discipline, precision, and structure. Painting encourages freedom, creativity, and self-expression.

What started as a pastime eventually became something more meaningful. There is now growing evidence that engagement with the arts, whether music, painting, literature, theatre, or other creative pursuits, has measurable benefits for emotional well-being. I have become very interested in that intersection between art and medicine.

My advice to young physicians is to cultivate interests beyond their profession. These activities are not distractions from a successful career; they can help sustain it.

KK: What is the core philosophy you strive to instill in your fellows as they prepare for the highly demanding world of ophthalmic oncology?

BE: If I had to identify one guiding principle, it would be simple: always do right by the patient. It sounds obvious, but it truly is the most important principle in medicine. If patient welfare becomes the driving force behind every decision—from where you work, to how you practice, to the choices you make in difficult clinical situations—then everything else tends to fall into place.

From an academic perspective, I place equal emphasis on integrity. Scientific discoveries must be pursued with honesty and transparency. Research should be driven by truth rather than recognition. I also believe strongly in collegiality. As our careers mature, it becomes increasingly important to acknowledge the contributions of those who came before us, while also taking appropriate ownership of our own work.

In today's world, information is everywhere. Artificial intelligence and digital tools can generate knowledge rapidly. What will distinguish physicians is not simply information, but our humanity—our experience, compassion, judgment, and ability to connect with patients. Those qualities are irreplaceable, and they are what I hope every fellow carries forward.

With her fellows at the Orbital Oncology Symposium 2017

My advice to young physicians is to cultivate interests beyond their profession. These activities are not distractions from a successful career; they can help sustain it.

Dr. Esmaeli with the faculty and former fellows of MD Anderson Cancer Centre

KK: Outside of oncology and research, what interests continue to inspire and energize you?

BE: The arts have become an important part of my life. I enjoy visual arts, music, opera, ballet, and especially choral music. Singing in a choir is something that comes very naturally to me and provides tremendous joy.

I also enjoy travel, reading, cooking, and spending time with friends and family. In recent years, I have become more committed to exercise and maintaining physical well-being. Having greater control over my schedule has allowed me to prioritize activities such as swimming and strength training.

I remain open to new experiences. In fact, one of my long-term aspirations is to spend more time gardening. I hope someday to have a home in San Diego, close to my family, where the climate is ideal for horticulture. I think there is something deeply rewarding about continuing to learn and explore new interests throughout life.

KK: Looking back, what is the central lesson from your journey?

BE: Challenges are inevitable. Whether they involve immigration, career transitions, institutional obstacles, or personal circumstances, every challenge carries the potential for opportunity.

If there is one recurring theme in my life, it is this: when unexpected difficulties arise, do not focus solely on what has been lost. Instead, look for what can be built. Many of the most meaningful achievements

in my career grew out of situations that initially appeared to be setbacks.

For young ophthalmologists, I would encourage curiosity, resilience, and the courage to think independently. Those qualities will serve you well, both professionally and personally.

******

Dr. Bita Esmaeli's career demonstrates how perseverance, innovation, and compassion can shape an entirely new subspecialty. From overcoming personal and professional challenges to pioneering advances in orbital oncology, her story offers valuable lessons for ophthalmologists at every stage of their careers. Above all, her journey reminds us that excellence often emerges not despite adversity, but because of how we choose to respond to it.

If there is one recurring theme in my life, it is this: when unexpected difficulties arise, do not focus solely on what has been lost. Instead, look for what can be built. Many of the most meaningful achievements in my career grew out of situations that initially appeared to be setbacks.

The Mentor and The Mentee: Dr. Bita Esmaeli with Dr. Kirthi Koka after the completion of her observership at MD Anderson Cancer Centre

Eyewitness

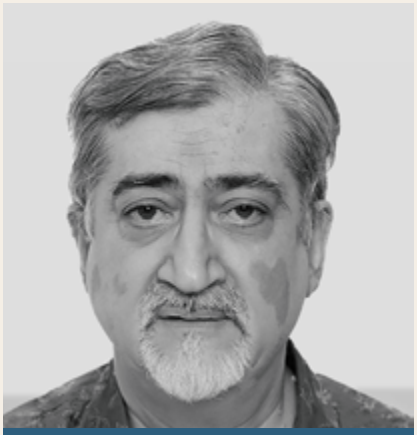
I AM THE EARS WITHOUT SOUNDS
I AM THE EYES WITHOUT BEING SEEN
I WEAR MY SPOTS WITHOUT BEING SPOTTED
I AM THE SPIRIT OF THE FOREST GREEN.

Creative candour by the experienced souls.

DIVYANSH K. MISHRA
LEOPARD
BANDIPUR TIGER RESERVE
KARNATAKA, INDIA

A Tiger's Tale

SANJIV DESAI



Dr. Sanjiv Desai
is the Medical Director of a non profit eye hospital in Jodhpur, where he balances outpatient care, surgery, free eye camps, and administration. Beyond the hospital walls, he finds joy in flying RC aeroplanes and launching model rockets skyward. And every couple of years, when life's weight grows heavy, he trades desert sands for ocean waves, taking a beach break and plunging into the quiet wonder of scuba diving.

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Have you ever stared into the blazing eyes of an angry tigress and lived to tell the tale ?

This is no campfire yarn. It happened to me. Read on…

Paradise and a Predator

Some years ago, I had taken a trip to Koh Samui, Thailand. It is an island off the east coast of the Thai mainland – a tropical paradise of swaying palms and turquoise seas. I was there to take an open water divers' course and become a certified scuba diver. Little did I know that I would also end up in a life-and-death tussle with a tigress.

It was late afternoon when I checked myself into a deluxe cabin at a swanky beach resort; palm fronds swaying, waves whispering. By nightfall my frugal instincts prevailed - after all, a few dollars saved equals a few beers earned! So, I requested the management to move me to a cheaper standard cabin. They obliged. It was in the dark of the night that the bell boy escorted me to a small cabin in another part of the resort which is reserved for the riff-raff.

The next morning, stepping out of my new digs, I was greeted by a most surreal sight: a log-fenced enclosure, about 20 feet square, right outside my cabin door. In the centre, leashed to a palm tree, sat a majestic tigress. Four tiger cubs and two leopard cubs tumbled around her. It was a spectacle more suited to Kipling than a holiday brochure. The resort owner, who doubled as their keeper, confirmed the big

One instant I was smiling at the cub, the next I was pinned beneath a mountain of muscle and fury.

They say one's entire life passes in a flash before a man dies.

cat's gender while serving breakfast to this royal family.

The Cub's Innocence

I was enchanted. The cubs played like kittens, and I longed to join them. I begged the owner to let me inside the corral (what else do you call a tiger pen?), but he refused. Still, I lingered at feeding times like the other guests, to watch the cubs play and pester the poor owner. On the third day, I told him he was missing a golden business opportunity to monetize the experience: let resort guests pose with the cubs for photos for a fee. He was tone deaf to my suggestion.

Incredulously, the next morning, a sign appeared on the fence "Photo with Tiger: 200 Baht." Surely, the Angel of Yenom must have worked her magic on him the night before and if you ask me, extra moolah never harmed anyone. Naturally, I cornered him and demanded free pictures for using my idea. He relented and with a wide grin, opened the wooden gate, asking me to step inside. At that point I felt like a child stepping into a forbidden kingdom.

So, there I was, seated beside a tigress. A blue towel was placed on my lap, a tiger cub gently lowered upon it, and a feeding bottle handed to me. The cub's fur was warm and its paws impossibly soft. The exercise was to feed milk to the baby. I held the feeding bottle, and the cub latched on greedily, tugging with surprising strength. Its tiny jaws worked furiously, milk dribbling down its whiskers and in my lap. I stroked its head, marvelling at the innocence of this miniature predator. Bliss! As I fed the baby, the owner clicked away with my Nikon, immortalizing my moment of triumph.

The Tigress' Fury

But paradise lasted only seconds. The leopard cubs, jealous of the attention, clawed at my legs. Their playful swipes were nothing compared to what followed. In a flash all hell broke loose.

In a blur of orange and black, the tigress lunged. One instant I was smiling at the cub, the next I was pinned beneath a mountain of muscle and fury. Her claws dug into my left knee and both feet. The weight of her massive body crushed me into the chair, every rib protesting. My face hovered inches from hers. Her hot breath blasted my face, fetid and suffocating. Her eyes - blazing orbs of fury - locked onto mine. She snarled, a guttural rumble that shook my bones, then erupted into a roar so close it rattled my skull and I almost died. In that moment I was certain I had become the tiger's meal and this was my last moment in paradise. I could almost feel her deciding how to finish me off – by slashing at my face with the free raised paw, or by gnawing at my jugular.

They say one's entire life passes in a flash before a man dies. It's happened to me once in my schooldays when I was drowning in a lake, but that's a story for another time. This time, strange as it sounds, two thoughts flashed by in my mind: one, I realized what the word "petrified" actually meant because that's what I was at that moment. Secondly, I remembered my bosom pal Vijay's advice that in times of trouble one must recite the "Hanuman Chalisa" for quick absolution of trouble. But the words just didn't come to me. Yes, I was truly petrified - my body and mind had become inanimate.

Saved by a Leash

Luckily, the adamantine chain was just long enough to keep the tigress 2 inches from my face and strong enough to hold her there.

Then, salvation came quickly. The owner sprang into action, dropping my SLR camera (miraculously unharmed),

It was pure maternal instinct guiding her. She was not concerned about me and was not actually attacking me - she was just protecting her own - which, in hindsight, was my salvation.

yanking the leash, shouting in a high-pitched staccato Thai. He stroked her flank, coaxing, pleading, soothing. The tigress resisted, snarling again, her teeth bared inches from my throat. Finally, with a violent tug, he succeeded in pulling her back.

I staggered up, shaking like a leaf, blood seeping from claw marks, my legs barely holding me. I stumbled into my cabin, shaken to the core but clutching my Nikon like a talisman. I tended to my wounds as best as I could and later ventured out of the cabin to thank the owner for saving my life.

The owner explained that the tigress was not attacking me out of malice. She feared the leopard cubs might harm her baby. It was pure maternal instinct guiding her. She was not concerned about me and was not actually attacking me - she was just protecting her own - which, in hindsight, was my salvation.

The Scar That Remains

My wounds festered, saltwater from the diving lessons slowing their healing. A scar remains etched on my left knee, a permanent souvenir of this misadventure. In family lore, the tale has grown legendary. I am now cast as a hero, a modern-day Sher Khan or Jim Corbett. And yes, whenever I retell the story, I sprinkle a little *"namak-mirch"* for flavor. But not today. This is the raw, unvarnished truth. Believe it.

Here I am, feeding a tiger cub, its tiny paws resting on my lap, its eager jaws tugging at the bottle. Just beyond the frame, about ten feet away, the tigress looms, chained to a palm tree. She's invisible in the picture, but very much present, her watchful presence adding a hidden tension to this seemingly tender moment.

The Unsung Hymn

KAVITA PORWAL

Dr. Kavita Porwal
is an ophthalmologist specializing in Paediatric Ophthalmology and Strabismus, with over 20 years of experience in clinical practice, surgery, and academics. She has trained at leading institutes including Aravind Eye Hospital and the M and J Institute of Ophthalmology. Her work focuses on managing complex paediatric eye disorders, strabismus, amblyopia, congenital cataracts, and myopia control. She is actively involved in teaching, and research, and currently serves as visiting Senior Consultant at C.H.L. Hospital and Macretina, Indore.

Email: *drkavitaporwal@yahoo.co.in*

Dedicated to my son

As a seed sleeps in its earthen bed,
No whisper tells what crown it's bred;
No hint of branch, no shade, no height,
No prophecy of bark or light.
So too the infant's tender face
Holds not a trace of future's grace;
No sign of sage with silvered breath,
Nor sorcerer weaving life and death.

The blossom, pale in morning's air,
Let's slip a fragrance soft and fair;
Majestic jasmine, white and mild,
Seems heaven's most obedient child.
Yet who could guess within its bloom
The mad embrace, the heart's perfume,
That binding spell, that sweet excess
Where love becomes its own duress?

Half the world has bowed to you,
In silent awe, in reverence true;
The other half, unmarked, unaware,
Or armored well in reason's care,

Stands distant from your mystic art,
Resisting conquest of the heart.

Of all man's cunning, carved and wrought,
From earth's deep breast by hunger sought,
From grain and gold, from flame and field,
From secret ores the mountains yield,
You rise beyond them, fierce and bright,
A faith no drought nor doubt can blight;
An unquenched salt upon the tongue,
A hymn forever yet unsung.

You veil the lord of morning's flame;
At dawn, the faithful speak your name.
For when the eastern skies are spun,
Daybreak is you,
And not the sun.

Control X: *Redo, Then Next*

KIRTI SINGH

Dr. Kirti Singh
is the Former Director and Professor of Ophthalmology at Guru Nanak Eye Centre, Maulana Azad Medical College, New Delhi. Dr. Singh graduated from Lady Hardinge Medical College with distinction and completed her postgraduation from Dr. R.P. Centre AIIMS, DNB, FRCS(E), and Glaucoma Fellowship from Wills Eye Hospital, USA. She has over 100 publications, and textbooks in Glaucoma and Contact lens including 15 book chapters. She has conducted several AIOS and state level workshops and lectured extensively. Dr. Singh is the recipient of several awards and honours including the Commonwealth Fellowship, Moorfield Hospital, London, WHO Fellowship, Aravind Eye Hospital, Madurai, and AIOS Fellowship 1999 at LVPEI, Hyderabad. A distinguished teacher, she has served as Treasurer DOS, Editor Delhi Journal Ophthalmology (2022-24), and Delhi State Nodal Officer, NPCB (2021-2023). Dr. Singh has also authored a volume of English poetry and was an Honorary radio compere for All India Radio and Doordarshan for eye health.

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If only the CTRL X option existed in real life
Erase the bad memories, paint vibrant colours anew.

Undo decisions wrong, explore opportunities afresh
Canvas regaining its vigor, it's clarity.

Remove all hurts, cull from very roots all
As if the wounds were never there.

Write down new thoughts, banish the stale
Press CTRL X. Start anew the next.

An inquisitive imp peeped in, read my words and held my pen.

Stop, re-read, introspect
The words hold the answer.

CTRL X, is daily placed along your morning tea
Wake up, script anew,
Discard old baggage, clean your cupboards.

Dawn does it daily
So perfectly, so completely
Why not you?

Computer keys are not the only tools
Our psychology is replete with shortcuts such.

Surgeon's Parallels

NIDHI PANDEY

Dr. Nidhi Pandey
I am an Oculoplasty Consultant and Head of Oculoplasty Services at IGHERC, Lucknow. I enjoy writing poetry based on my experiences.

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The vision of vicarious surgical bleeds
Paints hundred spouted fountain from Caeser.
The yo-yoing autoimmune conditions
Like Sisyphus' unyielding tryst.
No truer proving ground than the ORs
For Murphy's 'can and will go wrong' law.
Dropped nucleus sinking into the vitreous
How Alice descends the rabbit hole.
Between intubations and extubations
Schrödinger cat's suspension.
Warriors cloaked in gowns and masks
Tolkien's wanderers, wandering but never lost.
Taking the stage as mere actors
Us surgeons in our theatres!

Lose Thyself O' Trekker

SHEETAL SAVUR

Dr. Sheetal Savur
is Professor and Head of Department of Ophthalmology, Yenepoya Medical College, with two decades of dedicated service to patients and students. Beyond the clinic and classroom she finds meaning in nature, adventure, words, reflection and creativity. Dr. Savur believes in experiencing life wholly. Hence, along with academics, she has honed her skills as a national level table tennis player and as a national level trekker. She also dabbles in poetry. She believes medicine sharpens the mind, while poetry nourishes the soul. She brings not only the precision of an ophthalmologist, but also the sensitivity of a poet, seeking to illuminate vision in life and verse.

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I walk the trails
Neither for prowess nor praise.

I trek to lose myself
And in losing, I find myself again.

Whether I wield the knife or the pen
'I' here becomes unimportant.

Sans regret and worry I tread
Burying the ego, lightening the journey ahead.

While I walk, I unite with mirth
With the sun, wind and the earth.

I become the clouds and the rainfall
Then I become the roaring waterfall.

I become the bird and the bee
I become the flower dancing in glee.

The walk heals and mends the weary heart
Unearths the strength that was always a part.

And now the challenges of life seem less daunting
The mind is clear, no more fears haunting.

Eye Rest My Case

SWIFT AND STEADY
WINS THE RACE

A point-counterpoint perspective.

SANJAY JAISWAL
CHEETAH
MASAI MARA, KENYA

Chemotherapy in Retinoblastoma – *Evolution, Revolution, Coexistence or Replacement?*

Moderator: Santosh G. Honavar

For the Motion, "The era of intravenous chemotherapy in the management of Retinoblastoma is coming to an end": David H. Abramson

Against the Motion, "Intravenous chemotherapy is still relevant and necessary in the management of Retinoblastoma": Carol L. Shields

Dr. Santosh G. Honavar
is the Director of Ocular Oncology and Ophthalmic and Facial Plastic Surgery at Centre for Sight, Hyderabad and the Director of the National Retinoblastoma Foundation. He is the President of the International Society of Ocular Oncology. Dr. Honavar completed his postgraduation from Dr. R. P. Centre for Ophthalmic Sciences, AIIMS, New Delhi followed by Fellowship in Ocular Oncology in Wills Eye Hospital, Philadelphia. He established the Ocular Oncology Service and headed the Department of Ophthalmic Plastic Surgery at L.V. Prasad Eye Institute. He has served as the Editor of the Indian Journal of Ophthalmology and is the Honorary General Secretary of the AIOS. He has played an impactful role in standardization of ophthalmology training with structured residency and fellowship programmes. The postgraduate teaching programme, iFocus, is his brainchild. Dr. Honavar is the recipient of the Shanti Swarup Bhatnagar Award by the Government of India, the Lifetime Achievement Award by the American Academy of Ophthalmology and the Honorary Fellowship of the Royal College of Ophthalmologists, London.

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Dr. Honavar: Very few advances in ophthalmic oncology have transformed the clinical practice as dramatically as chemotherapy for retinoblastoma. Before the mid-1990s, treatment options were limited to enucleation and external beam radiotherapy. While effective for life salvage, these approaches often came at the cost of cosmesis, quality of life, and, in the case of radiotherapy, an increased risk of second malignant neoplasm (SMN).

The introduction of neoadjuvant intravenous chemotherapy (IVC) in mid-1990s ushered in a paradigm change in the management of retinoblastoma. IVC combined with focal therapy readily became the standard of care. For the first time, many eyes that would previously have been enucleated could be salvaged, radiotherapy could be avoided, and bilateral disease could be managed more effectively. A generation of ocular oncologists witnessed a transformation that was nothing short of revolutionary.

The next revolution emerged in the early and mid-2000s with the development of intraarterial chemotherapy (IAC). By delivering chemotherapy selectively into the ophthalmic artery, IAC achieved markedly higher intraocular drug concentrations while minimizing systemic exposure. Numerous studies have demonstrated superior eye salvage rates for Group D and selected Group E eyes with IAC.

The success of IAC has generated an important and increasingly polarized question: Has IVC become obsolete?

The answer is not straightforward. The debate extends beyond tumour control and eye salvage. It encompasses patient survival, prevention of metastasis, protection against trilateral retinoblastoma, systemic toxicity, health-care infrastructure, treatment accessibility, affordability, and global equity.

In high-income countries with established interventional neuroradiology programs, IAC is considered the first-line treatment for advanced unilateral disease and in appropriate cases of bilateral disease. In contrast, for many low- and middle-income countries, where children

Importantly, this is not a debate between past and future, nor between right and wrong. Rather, it is a thoughtful discussion between two masters of the discipline who share the same goal: saving children, preserving eyes, and maximizing vision.

Dr. David H. Abramson
is the founding Chief of Ophthalmic Oncology at Memorial Sloan Kettering Cancer Center where he is a tenured Professor of Surgery, Pediatrics and Radiation Oncology and Professor of Ophthalmology at Weill/Cornell Medical Center. He has published more than 800 papers and received many awards including the Lifetime Achievement Award from the AAO, Weisenfeld Award from ARVO, Helen Keller Research Award and the Indian Centre for Sight - National Retinoblastoma Foundation Oration 2013 and Medal of Honour.

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frequently present with advanced disease and access to IAC remains limited, IVC remains the backbone of retinoblastoma care because it is widely available, relatively inexpensive, and deliverable through the existing standard pediatric oncology infrastructure.

Emerging evidence suggests potential advantages of IAC in reducing systemic toxicity, avoiding carboplatin-associated ototoxicity, shortening treatment duration, and minimizing exposure to etoposide. Conversely, proponents of IVC emphasize its systemic protective effects, reduction in metastatic disease and trilateral retinoblastoma, ease of administration, and proven long-term outcomes and safety profile extending beyond two decades.

In this article, two giants of ocular oncology present opposing views on a provocative question:

"Is the era of IVC in retinoblastoma treatment coming to an end?"

Arguing that the era is ending is Dr. David Abramson, whose pioneering work helped establish IAC as a transformative treatment for retinoblastoma.

Arguing that IVC is here to stay is Dr. Carol Shields, whose contributions were instrumental in establishing IVC as a global standard and whose long-term data continue to define outcomes for modern retinoblastoma care.

The discussion that follows is particularly compelling because it is led by two individuals who have each helped shape a defining era in retinoblastoma management. Importantly, this is not a debate between past and future, nor between right and wrong. Rather, it is a thoughtful discussion between two masters of the discipline who share the same goal: saving children, preserving eyes, and maximizing vision. Their perspectives reflect not only differences in therapeutic preference but also broader considerations of evidence, accessibility, economics, and global applicability. **The challenge for us is not to identify a single winner, but to determine which strategy best serves each child and family in a rapidly evolving therapeutic landscape.**

IS THE ERA OF INTRAVENOUS CHEMOTHERAPY IN RETINOBLASTOMA TREATMENT COMING TO AN END?

Dr. Abramson: Definitely YES and definitely NO.

No: Intravenous chemotherapy is of paramount importance in addressing retinoblastoma when it is outside the eye. Careful prospective multi-institutional studies have shown that when retinoblastoma is documented to be outside the eye (orbit, optic nerve, hematogenous and rarely CNS metastases) not only does systemic chemotherapy (sometimes combined with radiation) prolong life but it may enable permanent cures.[1] Until better and safer alternatives come along, systemic chemotherapy (sometimes with radiation) is the standard of care for extraocular retinoblastoma worldwide. Intraarterial chemotherapy alone has been successful in select cases of optic nerve disease and orbital disease and its role in the future is exciting.[2-4]

YES: Systemic chemotherapy for retinoblastoma is not only coming to an end in many, many centers worldwide… it has already ended in most. In the largest retinoblastoma center in the U.S. (at MSKCC) ***we have not used radiation or systemic chemotherapy for retinoblastoma in 20 years*** except for very young patients (first 3 months of life) where for a number of years we gave modest single agent doses of intravenous

Until better and safer alternatives come along, systemic chemotherapy (sometimes with radiation) is the standard of care for extraocular retinoblastoma worldwide.

Intraarterial chemotherapy is more effective (saves more eyes, saves more vision), is faster to cure, avoids more enucleations, and is less toxic than multiagent systemic chemotherapy.

Carboplatin to shrink tumors before definitive treatment with intraarterial chemotherapy (called "bridge therapy"). We abandoned that years ago because, with experience, we have been able to treat those small infants primarily with intraarterial chemotherapy.[5]

Think about that - 20 years with no radiation or systemic chemotherapy for intraocular disease! And it is not just our center; now that approach is strongly supported by many studies. There are now hundreds of papers from literally almost every continent and many meta-analyses and every single one agrees that intraarterial chemotherapy is more effective (saves more eyes, saves more vision), is faster to cure, avoids more enucleations, and is less toxic than multiagent systemic chemotherapy. Some even concluded that metastatic rates were lower after intraarterial chemotherapy.[6] No paper has suggested that by treating advanced intraocular retinoblastoma by leaving the eye in and doing intraarterial chemotherapy that patient survival is compromised, but some metanalyses have concluded that patient survival is higher in the eyes that had intraarterial chemotherapy.[6]

Critics have often pointed out that these many studies were not randomized so there may be selection bias, but clinicians know that in the era of intraarterial chemotherapy **many more advanced eyes are saved** so it is unlikely that bias is the explanation (in other words more, not less, advanced eyes are treated with intraarterial chemotherapy than intravenous chemotherapy).

Of course, no randomized trial ever compared enucleation or radiation to systemic chemotherapy for intraocular disease, but two excellent randomized trials have been published comparing intravenous chemotherapy to intaarterial chemotherapy. One study involved 234 patients.[7] They conclusively showed that there was no justification for using systemic chemotherapy for intraocular disease in the modern world. This study was done on patients with unilateral disease and because of the complexity of bilateral disease, it is unlikely that we will see a similar randomized trial on patients with bilateral disease, but again, in New York we simply treat both eyes with intraarterial chemotherapy in the same session and never use systemic chemotherapy and the results (ocular survival, patient survival and complications) are the same as unilateral patients.

Why is systemic chemotherapy disappearing (or has already disappeared) worldwide for the treatment of intraocular retinoblastoma?

1. For unilateral disease (primary or recurrent after systemic chemotherapy) many more eyes are saved. Also, true when bilateral cases are treated simultaneously ("tandem therapy").[8]

2. For unilateral disease far fewer eyes treated with intraarterial chemotherapy come to enucleation.

3. Treatment time is shorter for intraarterial chemotherapy (compared to intravenous).

4. Systemic toxicity is less.

5. Growth of the patient is not affected by intraarterial chemotherapy (this has not been studied in patients treated with intravenous chemotherapy, but retarded growth is common-often temporary with systemic chemotherapy).[9]

6. Immune system is not affected by intraarterial chemotherapy so children can be vaccinated during treatment and unlike patients treated with systemic chemotherapy continuous use

Immune system is not affected by intraarterial chemotherapy so children can be vaccinated during treatment and unlike patients treated with systemic chemotherapy continuous use of antibiotics is not necessary.

of antibiotics is not necessary.

7. Ports are not needed. This contributes to cost and infections.

8. Overall treatment is cheaper. More than one institution has shown that though intraarterial chemotherapy is costly on the day of treatment, because the children do not need ports, antibiotics, blood cultures (fever/neutropenia) or hospitalization for secondary infections the actual overall cost of intraarterial chemotherapy is less than intravenous.

9. The most potent and most commonly used drug intravenously is Carboplatin. Unfortunately, it causes hearing deficits from minor (high frequency loss) toxicity to children requiring full time hearing aids. While there is no complete agreement on the incidence of this problem, we have all seen it. Permanent hearing loss is more common for younger children. Two studies have now shown that **even though Carboplatin is used in intraarterial chemotherapy, hearing is unaffected.**[10]

Second cancers: The retinoblastoma community is well aware of the radiation related "second cancers" in patients (with germline disease) who received external beam irradiation. That is the main reason radiation has not been done in our center (and yours) for more than 20 years. Unfortunately, the drug Etoposide (a Topoisomerase II inhibitor) is routinely used when children get systemic chemotherapy. For intraarterial chemotherapy a Topoisomerase inhibitor is also used, but it is a Topoisomerase I inhibitor (and much lower doses). Topoisomerase II inhibitors in pediatric oncology are well known to cause a usually fatal secondary leukemia (sAML). Topoisomerase I inhibitors (such as Topotecan which is used in intraarterial chemotherapy) do not cause leukemia. Careful studies have shown that the use of Etoposide (Topoisomerase inhibitors II) systemically in retinoblastoma increases the chance of developing this (usually) fatal second cancer (leukemia) 140 fold.[11,12] Can you really sleep at night knowing you have done that to your little child with retinoblastoma? I could not. Can you go home at night and tell your family you knowingly did that?

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Topoisomerase I inhibitors (such as Topotecan which is used in intraarterial chemotherapy) do not cause leukemia.

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INTRAVENOUS CHEMOTHERAPY IS HERE TO STAY IN THE MANAGEMENT OF RETINOBLASTOMA - *FOREVER*

Dr. Carol L. Shields
completed her ophthalmology training at Wills Eye Hospital in Philadelphia and Fellowship training in Ocular Oncology, Oculoplastic Surgery, and Ophthalmic Pathology. She is currently Director of the Oncology Service, Wills Eye Hospital, and Professor of Ophthalmology at Thomas Jefferson University in Philadelphia. She has authored or co-authored 12 textbooks, 341 chapters in edited textbooks, over 2000 articles in major peer-reviewed journals, and given over 1000 lectureships. The most prestigious awards that have honored her include the Donders Award (2003) - given by the Netherlands Ophthalmological Society every 5 years to an ophthalmologist worldwide who has contributed to the field of ophthalmology. She was the first woman to receive this award. Her other laurels include the American Academy of Ophthalmology Life Achievement Honor Award (2011) for contributions to the field of ophthalmology, Theodore Roosevelt Award - the highest honor the National Collegiate Athletic Association (NCAA) confers on an individual who earned a varsity letter for sports in college and who became a distinguished citizen of national reputation and induction into the Academic All-American Hall of Fame (2011) for lifetime success in athletics and career. She was the President of the International Society of Ocular Oncology (2013-2015). She has been included in the Ophthalmology Power List 2014-2023 – Nominated by peers as one of the top 100 leaders in the field of ophthalmology. Dr. Carol Shields is a member of numerous ocular oncology, pathology, and retina societies. She serves on the editorial or advisory board of 31 journals, including JAMA Ophthalmology and RETINA. Each year the Oncology Service manages approximately 500 patients with uveal melanoma, 120 patients with retinoblastoma, and hundreds of other intraocular, orbital, and conjunctival tumors from the United States and abroad.

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Dr. Shields: There is no doubt in my mind that intravenous chemotherapy (IVC) has revolutionized the management of retinoblastoma worldwide. ***No doubt at all.*** Prior to IVC, children with retinoblastoma would have either had enucleation or external beam radiotherapy as management. Prior to IVC, children with retinoblastoma would have gone through life with a missing eye, or both eyes missing in blindness, wearing prosthesis (prostheses), or a deformed face with dry eye, cataract, retinopathy, and blindness from radiotherapy and at risk for second cancers. Their entire life would be with cosmetic deformity, and with risk for metastasis and death. ***That stinks! That's no way to live a life.*** Now, IVC changed that in a big way, and in my mind, IVC was perhaps the greatest, most convincingly magnificent change in the management of retinoblastoma – of all times. The use of IVC has allowed children to achieve control of retinoblastoma and avoid enucleation, avoid external beam radiotherapy, avoid trilateral retinoblastoma, avoid metastatic disease, and at a cost that is affordable.

The science behind intravenous chemotherapy

The use of IVC dates back to 1994 when the regimen of vincristine, etoposide, and carboplatin for retinoblastoma was explored by Dr. Judith Kingston, a pediatric oncologist in London, England, and quickly 4 centers, including Toronto Canada, Los Angeles USA, Philadelphia USA, and London England, realized the success of this chemotherapy for retinoblastoma and started using this regimen.[1] In 1996, the first 4 reports were published in the Archives of Ophthalmology on the topic of IVC for retinoblastoma from these select retinoblastoma centers and an editorial was written and entitled ***"A New Era for the Treatment of Retinoblastoma"***.[2-6] And gosh, this editorial was correct – this was an incredible era for retinoblastoma management. We now have 32 years follow up on IVC for retinoblastoma and we have documented that this chemotherapy definitely does work, the results vary based on the International Classification of Retinoblastoma, and this chemotherapy regimen can be curative, lasting decades. We anticipate that this therapy is curative and ***lasts a lifetime.***

When we give IVC for retinoblastoma we provide 3 agents, including vincristine, etoposide, and carboplatin every month for 6 months with focal consolidation at each monthly visit. All patients receive the same protocol, and it is adjusted by kilogram weight. The IVC can cure the intraocular retinoblastoma and we always consolidate the regressed tumor with thermotherapy or cryotherapy, ***AND*** it can also reduce the risk for pinealoblastoma and systemic metastasis. In 2020, our team published long-term 20-year real world outcomes of IVC for retinoblastoma in 964 eyes of 554 patients at our center and noted that this six-month treatment was lasting at 20 years with complete control and globe salvage for Group A retinoblastoma at 96%, Group B at 90%, Group C at 90%, Group D at 68%, and selective Group E at 32%.[7-10] Those that fail IVC are often managed with IAC, intravitreal chemotherapy, plaque radiotherapy, or enucleation.

Why is IVC for retinoblastoma here to stay?

Below is a list of reasons why I believe IVC is here to stay.

Basically, ***IVC can save the child's life, the child's eye, and even save the***

In my mind, IVC was perhaps the greatest, most convincingly magnificent change in the management of retinoblastoma – of all times.

The IVC can cure the intraocular retinoblastoma and we always consolidate the regressed tumor with thermotherapy or cryotherapy, AND it can also reduce the risk for pinealoblastoma and systemic metastasis.

child's vision.

1. IVC for retinoblastoma can be given by a pediatric oncologist anywhere in the world.

2. IVC for retinoblastoma has ***some hidden properties*** that allow children with retinoblastoma to live and these include:

   a. IVC can prevent metastatic disease, and this is important, especially in low-income countries as children may have more advanced disease at risk for metastasis. [11-13] IVC has clearly been shown to prevent metastasis. [11,12]

   b. IVC can prevent trilateral retinoblastoma and this is important as 8% of germline mutation patients (typically bilateral retinoblastoma) are at risk for trilateral retinoblastoma (pinealoblastoma) which can lead to death. [14-17] IVC can prevent this highly-fatal tumor. In our experience over the past 32 years using IVC for retinoblastoma, we had only one case of trilateral retinoblastoma in our series of over 700 consecutive patients and that was early-on when we started using IVC. In the past 25 years, we have seen no case of trilateral retinoblastoma in children using IVC for retinoblastoma.

   c. IVC can cure retinoblastoma in both eyes at the same time and save the eyes with some vision.

   d. IVC can restore vision in some children with retinal detachment as the chemotherapy can resolve the detachment and the vision returns.

3. IVC is affordable.

4. IVC is far more wide-spread in use, easy to set-up in a clinic and administer, and so much more affordable than IAC.

So there you have it – IVC for retinoblastoma can save the child's life, eyeball, and vision.

What are the side effects of IVC?

The main side effect of IVC is that it drops the blood count approximately two weeks after the chemotherapy is administered, but that recovers to normal. Other side effects include hearing toxicity and renal toxicity, but if the drugs are given correctly, these toxicities can be avoided. As with all chemotherapy, there is a risk for leukemia, and we have only seen 1 case in our 32-year experience with over 700 children treated with IVC for retinoblastoma.

In experienced hands, the delivery of IVC is typically without complications. Children survive and maintain a normal life with no facial dysmorphism, like the old days. They are able to reproduce at an older age with no effect of chemotherapy on fertility.

Now compare the side effects of IVC to those from IAC. IAC can lead to abrupt loss of vision, neovascular glaucoma, chronic retinal detachment, vitreous hemorrhage, retinal hemorrhage, retroperitoneal hemorrhage, loss of the eye, brain infarction (stroke), and death. And also keep in mind that IAC requires an extremely skilled interventional neuroradiologist or neurosurgeon to perform the catheterization and delivery of the medication through the ophthalmic artery. The learning curve is sharp and complications parallel the learning curve.

Why is IVC necessary in the management of retinoblastoma?

IVC is necessary in the management

IVC is far more wide-spread in use, easy to set-up in a clinic and administer, and so much more affordable than IAC.

of retinoblastoma because it is a straightforward, easy to provide therapy to cure the eye cancer and save the child from death.[18] **Period.** There are other methods to treat retinoblastoma, such as IAC, intravitreal chemotherapy, plaque radiotherapy, external beam, radiotherapy, and enucleation, but we prefer IVC for starters, especially for bilateral germline mutation retinoblastoma. Yes, we use IAC extensively in our practice, but it is expensive, requires a competent neurosurgeon, and it can cause complications. Complications are now uncommon with IAC in our hands but years ago when we started IAC we had to deal with several problems. Do not get me wrong – IAC is a good therapy for retinoblastoma, but we use it with caution.

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THE FINAL WORD

BEYOND THE DEBATE: WHAT TRULY MATTERS IN RETINOBLASTOMA CARE

Dr. Honavar: This debate elegantly captures the beautiful evolution in the management of retinoblastoma in recent times. Reading the perspectives of Dr. Abramson and Dr. Shields, one is struck less by the disagreement than by the extraordinary journey that retinoblastoma management has undertaken over the past three decades. **Both authors have played seminal roles in shaping that journey. Both have transformed the lives of countless children and their families. And both are arguing from positions built on immense clinical experience, scientific rigor, and an unwavering commitment to better outcomes.**

The question is whether IVC should continue to occupy a central role in the management of intraocular retinoblastoma.

Dr. Abramson argues that for many patients, particularly those treated in specialized centres, the answer is increasingly no. The evidence supporting IAC continues to grow. Comparative studies, meta-analyses, and clinical experience from leading centres consistently demonstrate superior eye salvage, reduced systemic toxicity, shorter treatment duration, and favourable long-term outcomes. From this perspective, IVC is becoming a historical bridge between the radiotherapy era and the era of anatomically targeted therapy.

The evidence supporting IAC continues to grow. Comparative studies, meta-analyses, and clinical experience from leading centres consistently demonstrate superior eye salvage, reduced systemic toxicity, shorter treatment duration, and favourable long-term outcomes.

Dr. Shields eloquently reminds us that the story is more complex. Retinoblastoma is not merely an eye disease; it is a childhood cancer. Treatment success cannot be measured solely by eye salvage rates. IVC has accumulated more than three decades of outcome data, can be administered in virtually any pediatric oncology unit, is considerably more accessible worldwide, and may confer systemic protection against metastatic disease and trilateral retinoblastoma. For much of the world, it remains the most practical and effective treatment platform available.

Both perspectives are valid.

Indeed, the answer may depend less on the biology of retinoblastoma than on the geography of retinoblastoma.

However, the answer is far from simple.

Retinoblastoma is not merely an eye disease; it is a childhood cancer. Treatment success cannot be measured solely by eye salvage rates.

More than 80% of children with retinoblastoma are born in low- and middle-income countries. For these children, survival remains the foremost challenge.

The choice between IVC and IAC should be guided by disease characteristics, patient factors, expertise, infrastructure, and access - not ideology.

Part of the complexity arises because retinoblastoma is unlike most other intraocular tumours. It is simultaneously an ocular disease, a pediatric cancer, a genetic disorder, a public health challenge, and, in many parts of the world, a victim of healthcare inequity. Success cannot be measured solely by eye salvage. Survival, vision, quality of life, treatment accessibility, affordability, abandonment, and long-term systemic outcomes are equally important considerations.

The debate becomes even more nuanced when viewed through a global lens. In New York, Philadelphia, London, Tokyo, Lausanne, or other highly specialized centres, the question may legitimately be whether IAC should completely replace IVC as first-line treatment for retinoblastoma. In large parts of Asia, Africa, and Latin America, where children often present late, resources are constrained, and access to interventional neuroradiology is limited, the more pressing question remains whether every child can access timely and effective treatment at all. This distinction is critically important. More than 80% of children with retinoblastoma are born in low- and middle-income countries. For these children, survival remains the foremost challenge. Treatment abandonment, delayed diagnosis, advanced presentation, and inequitable access to care continue to account for more morbidity and mortality than the choice of chemotherapy delivery route. Importantly, if magnetic resonance imaging (MRI) with contrast is not part of the baseline evaluation protocol, critical risk factors such as large choroidal invasion and optic nerve infiltration can be missed. In such situations, IVC is likely to confer protection against systemic metastasis.

History teaches us that progress in retinoblastoma has rarely occurred through replacement alone. Enucleation was not eliminated by radiotherapy. Radiotherapy was not completely replaced by chemotherapy. Instead, each advance expanded our therapeutic armamentarium and refined our ability to tailor treatment to individual patients. The future of retinoblastoma is therefore unlikely to be binary. Rather, it will belong to personalized, risk-adapted, multidisciplinary care - integrating IVC, IAC, intravitreal chemotherapy, focal therapies, genetics, molecular diagnostics, and emerging targeted approaches in a manner that is evidence-based, patient-centred, and globally relevant.

Areas of Consensus

Both authors agree that:

- Saving the child's life remains the highest priority.
- Chemotherapy has transformed retinoblastoma management and dramatically reduced dependence on external beam radiotherapy.
- IAC is a major therapeutic advance.
- IVC remains indispensable for extraocular, metastatic, orbital, and high-risk disease.
- Optimal outcomes require multidisciplinary care delivered by experienced teams.

Areas of Continuing Debate

- Should IAC become the preferred first-line treatment for advanced intraocular retinoblastoma?
- Does IVC provide unique protection against metastatic disease and trilateral retinoblastoma?
- How should efficacy be balanced against systemic toxicity, procedural risk, cost, and accessibility?

Ultimately, the measure of progress is not whether one treatment replaces another. It is whether more children survive, more eyes are preserved, more vision is saved, and more families are spared the devastating consequences of this disease with the best available care within the realities of each healthcare system. On that goal, there is no disagreement.

- Can the successes achieved in highly specialized centres be replicated globally?

Take-home Messages

- There is no debate that chemotherapy has revolutionized retinoblastoma care.
- IVC remains one of the most important advances in the history of retinoblastoma and continues to play a vital role worldwide.
- IVC may be preferred if MRI shows choroidal invasion.
- IAC has helped optimize eye salvage, specifically in group D and E retinoblastoma.
- The choice between IVC and IAC should be guided by disease characteristics, patient factors, expertise, infrastructure, and access - not ideology.
- The global retinoblastoma community must ensure that technological progress does not widen disparities in care.
- The future lies not in choosing between IVC and IAC, but in determining how best to deploy each for the benefit of every child.

So, is the era of IVC coming to an end? In centres with mature IAC programs, advanced imaging, experienced neurointerventional teams, and robust follow-up systems, the role of IVC for intraocular disease is undoubtedly shrinking. Yet in many parts of the world, IVC remains the cornerstone of retinoblastoma care. Ultimately, the measure of progress is not whether one treatment replaces another. It is whether more children survive, more eyes are preserved, more vision is saved, and more families are spared the devastating consequences of this disease with the best available care within the realities of each healthcare system. On that goal, there is no disagreement.

In the end, the true measure of progress is not the route by which chemotherapy reaches the eye, but the number of children who live to see the future.

RetroSpectacles

ASLAN, ALEX, MUFASA AND SIMBA
MANY NAMES THEY PRAISE AND SING,
TIMELESS TALES OF A NOBLE RULER
IT TAKES A JUNGLE TO RAISE A KING.

Eye through the ages.

MANISH NAGPAL
AFRICAN LION
MASAI MARA, KENYA

Two Hits, Two Lives

SHAIFALI CHAHAR

Dr. Shaifali Chahar
received her basic medical education from Kasturba Medical College, Manipal, and completed her post-graduate training at Sir Ganga Ram Hospital, New Delhi. Following a short observership at Moorfields Eye Hospital, London, she pursued a fellowship in Comprehensive Ophthalmology at Prabha Eye Clinic and Research Centre in Bangalore, and subsequently completed a long-term fellowship in Oculoplasty and Ocular Oncology under the mentorship of Dr. Santosh G. Honavar at Centre For Sight, Hyderabad. She received the gold medal in oculoplastic surgery awarded by FAICO. Currently, she serves as a Consultant in Oculoplasty and Ocular Oncology at HORUS Specialty Eye Care, Bangalore, Karnataka.

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Sometimes it takes "two" hits to change the beginning and end of a story…

A young couple sits across from a genetic counsellor.

The husband lost an eye to retinoblastoma as a toddler. He remembers none of it—only old photographs, a prosthetic eye, and stories told by his mother. Now he and his wife want a child of their own.

The counsellor draws a simple diagram. *"There is a gene called RB1,"* she explains. *"In hereditary retinoblastoma, one copy is already altered from birth. All it takes is one more genetic event in a retinal cell, and a tumour can develop."* Today, a blood test can identify the mutation. IVF embryos can be screened. Families can make informed decisions that would have been unimaginable a generation ago.

The couple exhales. They understand the importance of the results of this genetic test, how it can help them to be pre-emptive in their journey and not be blind-sided by a life-altering diagnosis.

What they may never know is that the science guiding that conversation began just fifty years ago with a physician who liked mathematics, a rare childhood eye tumour, and a question nobody else thought to ask.

Alfred G. Knudson Jr. was not searching for a cancer gene. In fact, when he began studying retinoblastoma in the late 1960s, nobody had ever identified a hereditary cancer gene. The RB1 gene had not been discovered. The term "tumour suppressor gene" did not even exist. But what Knudson had was a habit of looking out for new problems to solve and more importantly looking at them differently.

Born in Los Angeles in 1922, Knudson entered the California Institute of Technology intending to study physics. However, he soon became captivated by genetics, feeling that many of the great

There were no gene sequencing machines. There was no RB1 gene. There was only mathematics. Yet Knudson had predicted the existence of a cancer-causing mechanism years before technology could prove it.

Anna Meadows, a dynamic young paediatric oncologist at Children's Hospital of Philadelphia, later joked that she had fallen in love with Knudson's 1971 paper before she fell in love with the man himself.

questions in physics had already been tackled, while biology remained full of mysteries waiting to be solved. Hence, genetics captivated him. Under the influence of legendary geneticists such as Thomas Hunt Morgan and Alfred Sturtevant, he became fascinated by the idea that biology could be understood through patterns, probability, and careful observation. After medical school, paediatric training, military service, and a PhD in genetics and biochemistry, Knudson arrived at MD Anderson Cancer Centre in Houston with a growing interest in childhood cancers.

Retinoblastoma immediately caught his attention. It was, as he later described, a "simplifying condition" to study. Unlike adult cancers, which develop after decades of environmental exposures, retinoblastoma appeared in infancy. Some children developed multiple tumours in both eyes very early in life. Others developed a single tumour in one eye, usually later. The pattern was obvious. The explanation was not.

While most researchers focused on the tumour itself, Knudson being a mathematician at heart focused on the numbers.

He examined records of children with retinoblastoma and plotted their ages at diagnosis. He observed that children with familial retinoblastoma developed very early multiple tumours in both eyes, while patients with sporadic (non-familial) retinoblastoma developed a single tumour later and only in one eye. The resulting curves told a story. Children with hereditary retinoblastoma behaved as though they needed only one additional event to develop cancer. Children with sporadic disease behaved as though they needed two.

In 1971, Knudson published a deceptively simple paper proposing what would become one of the most influential ideas in cancer biology: the Two-Hit Hypothesis. His conclusion was revolutionary. A child with hereditary retinoblastoma is born carrying the first genetic "hit" in every cell of the body. Only one additional hit is needed in a retinal cell to initiate a tumour. In sporadic retinoblastoma, both hits must occur after birth in the same cell, making the disease less likely and typically later in onset.

There were no gene sequencing machines. There was no RB1 gene. There was only mathematics. Yet Knudson had predicted the existence of a cancer-causing mechanism years before technology could prove it.

The next chapter of his story began in Philadelphia.

A young paediatric oncologist named Anna Meadows was caring for a child with retinoblastoma and developmental delay. Suspecting something unusual, she requested chromosome analysis. The child was found to have a deletion on chromosome 13q14.The finding provided the first major clue to the location of the elusive retinoblastoma gene. The scientific collaboration soon became something more personal. Anna Meadows, a dynamic young paediatric oncologist at Children's Hospital of Philadelphia, later joked that she had fallen in love with Knudson's 1971 paper before she fell in love with the man himself. It was perhaps inevitable that two people captivated by the same scientific question would eventually find themselves writing the next chapters of the story together.

In 1976, Knudson moved to Philadelphia to lead the Institute for Cancer Research at Fox Chase Cancer Centre. The same year, he married Anna Meadows.

He indeed had had his life's "two hits."

Years later, Knudson affectionately described their interests by saying that he studied the "alpha" of RB1 while Anna studied its "omega." He studied the beginning of the story. She studied what came after.

Dr. Anna Meadows and Dr. Alfred Knudson at a fundraising gala in Philadelphia in 2005. (Bellacosa A, Chernoff J, Testa JR. Alfred G. Knudson (1922–2016). Cell. 2016 Aug 11;166(4):785-6).

At a time when researchers were searching for answers in tumours, Knudson searched for answers in patterns. He often warned against simply following the crowd, to not become a ' herd scientist'.

For the next four decades, they would study different ends of the same disease and thus, change the landscape of retinoblastoma together. Knudson investigated how retinoblastoma begins. Meadows became a pioneer in understanding what happens after children survive cancer—the late effects of treatment, second malignancies, and long-term survivorship. Their collaboration did not end in the laboratory. In Philadelphia, Al and Anna became known as a spirited "good cop–bad cop" team, challenging each other's ideas, refining each other's arguments, and leaving a lasting imprint on the city's scientific community. If retinoblastoma was their common language, curiosity was the bond that sustained the conversation. Together, they published on retinoblastoma, neuroblastoma, and childhood cancer survivorship.

Years later, Knudson affectionately described their interests by saying that he studied the "alpha" of RB1 while Anna studied its "omega." He studied the beginning of the story. She studied what came after.

And surprisingly, it took another fifteen years for biology to catch up with mathematics. In 1986, Stephen Friend, Robert Weinberg, and colleagues successfully cloned RB1, the first tumour suppressor gene ever identified. Knudson's prediction had been correct. The discovery transformed cancer research.

Until then, many scientists viewed cancer primarily as a disease caused by activated oncogenes—genetic accelerators stuck in the "on" position. RB1 revealed something equally important: cancer could arise when the brakes failed.

Soon came TP53, APC, BRCA1, BRCA2, and dozens of other tumour suppressor genes. What began as a study of a rare childhood eye tumour became a framework for understanding cancer itself.

Perhaps the deeper lesson from Knudson's story is not the two-hit hypothesis itself. It is the value of asking an original question. At a time when researchers were searching for answers in tumours, Knudson searched for answers in patterns. He often warned against simply following the crowd, to not become a ' herd scientist'—a reminder that scientific progress rarely comes from repeating what everyone else is already doing. It comes from noticing what everyone else has missed.

Perhaps that is why his story continues to resonate. He did not discover RB1 with a powerful machine. He did not have access to technologies that modern researchers take for granted. He simply noticed a pattern that others overlooked.

Alfred Knudson died in 2016 at the age of 93. Anna Meadows continued their valuable work until her passing in 2021.

Their legacy lives on every time a family receives genetic counselling, every time a child with retinoblastoma undergoes molecular testing, every time a scientist searches for the genetic origins of cancer, every time a child's life , eye and vision is saved by modern therapies and they live on to survive and have a full life in spite of being diagnosed with this potentially lethal disease.

Not bad for a discovery that began with a physician, a graph, and a willingness to count tumours. The lesson remains timeless: breakthroughs often begin when someone asks a familiar question in an unfamiliar way.

Suggested reading

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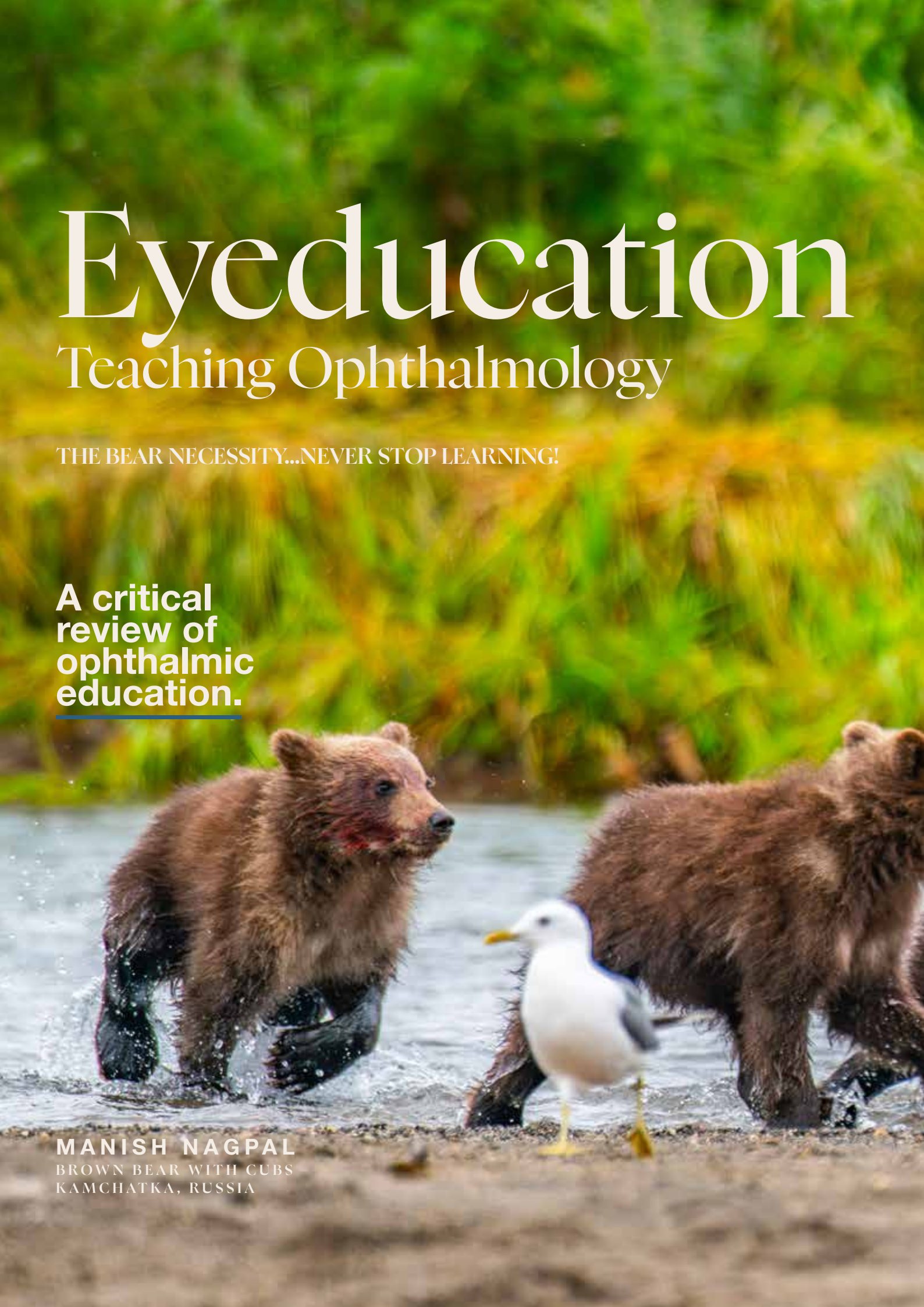

MANISH NAGPAL

BROWN BEAR WITH CUBS
KAMCHATKA, RUSSIA

Ocular Oncology for Residents – *Why, What and How Much?*

FAIROOZ P. MANJANDAVIDA

Dr. Fairooz P. Manjandavida
Founder and Director of HORUS Specialty Eye Care in Bengaluru, India, is a distinguished ophthalmic surgeon specializing in Ocular Oncology, Ophthalmic Plastic and Orbital Surgery. Recognized among the Top 100 Women Ophthalmologists globally, she established an Ocular Oncology Department at a Regional Cancer Center in her hometown of Kerala- a significant dream project that embodies her commitment to giving back to society. In addition to her clinical prowess, Dr. Fairooz is a dedicated educator and academician, actively involved in teaching and mentoring aspiring ophthalmologists. She completed her super-specialty fellowships at the L.V. Prasad Eye Institute and Wills Eye Hospital, Philadelphia, and is a Fellow of the Royal College of London and American College of Surgeons. A recipient of numerous prestigious awards, including the AAO and APAO International Achievement Award, she serves as the Vice President of the Asia Pacific Society of Ocular Oncology Pathology, contributing significantly to research and education in eye cancer management.

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"Not every resident will become an ocular oncologist. But every resident must become the kind of clinician who never ignores danger."

Every journey in medicine begins with a moment that initially appears ordinary. Mine began during residency at Mysore Medical College and Research Institute in 2006, when my unit head, the late Prof. Venkate Gowda, made a conscious effort to expose us to rare and often unseen diseases beyond routine ophthalmology during postgraduate teaching sessions. I was assigned the topic of Uveal Melanoma — a presentation that unknowingly became my PhD topic. Soon after, Dr. D. N. Prakash handed me a newly released book on Retinoblastoma. At the time, I accepted it simply as a super-enthusiastic resident eager to learn. Years later, I often reflect on those moments and wonder — was it coincidence, destiny, or perhaps the quiet beginning of a lifelong calling?

Ocular oncology is often perceived as a niche superspecialty encountered only in tertiary referral centers. While it may occupy a small proportion of clinical volume during residency, it plays a disproportionately large role in cultivating vigilance, diagnostic responsibility and multidisciplinary thinking. This is the kind of future clinicians that the world deserves.

During residency, the emphasis naturally falls on cataract, glaucoma, retina and corneal diseases because of their overwhelming clinical volume. Yet, hidden within routine ophthalmic practice are conditions that may threaten not only vision, but also life itself. A subtle conjunctival pigmentation, a recurrent "chalazion," a child with leukocoria, or unexplained proptosis may represent an underlying malignancy. For this reason, ocular oncology deserves an important place in residency training—not necessarily to create ocular oncologists out of every resident, but to create ophthalmologists who know when to suspect a tumor.

Why ocular oncology matters during residency

The importance of ocular oncology begins with its consequences. Unlike many ophthalmic conditions that primarily affect visual function, ocular tumors can carry systemic and life-threatening implications. Retinoblastoma, the most common intraocular malignancy in children, is a classic example where early diagnosis can mean the difference between life and death. Similarly, sebaceous gland carcinoma of the eyelid can masquerade as chronic blepharitis

A vigilant resident may become the first link in saving a patient's life.

Ocular oncology refines slit-lamp examination, indirect ophthalmoscopy, documentation skills and imaging interpretation.

In ophthalmology training, a resident may examine thousands of cataracts but only a handful of ocular tumors. Yet the consequences of overlooking a single malignancy can be devastating.

or recurrent chalazion, leading to delayed diagnosis and metastatic disease. Choroidal melanoma, though uncommon in some populations, remains the most common primary intraocular malignancy in adults and may metastasize years after ocular treatment. In such scenarios, the ophthalmologist is often the first physician to suspect the disease. A vigilant resident, therefore, may become the first link in saving a patient's life.

What residents need to learn

Ocular oncology teaches the art of observation. Residents frequently learn that oncology is not simply about identifying a mass lesion, but about recognizing patterns and subtle warning signs. For instance, a salmon-pink conjunctival lesion may suggest lymphoma, while a unilateral chronic red eye resistant to therapy may represent ocular surface squamous neoplasia. A choroidal lesion with orange pigment and subretinal fluid deserves far greater attention than a stable nevus. Ocular oncology refines slit-lamp examination, indirect ophthalmoscopy, documentation skills and imaging interpretation. More importantly, it teaches clinical suspicion—a quality that separates a careful clinician from a routine examiner.

One of the greatest misconceptions among residents is that ocular tumors are "rare" and therefore less relevant. However, rare diseases are often those most commonly missed. In ophthalmology training, a resident may examine thousands of cataracts but only a handful of ocular tumors. Yet the consequences of overlooking a single malignancy can be devastating. Therefore, the specialty emphasizes vigilance over volume. Even if residents do not encounter every tumor during training, they must know the red flags that warrant further evaluation or referral.

Key knowledge areas for residents

So, what exactly should a resident know in ocular oncology? The first and most essential aspect is recognition of warning signs. Every ophthalmology resident should be familiar with clinical clues such as leukocoria, unexplained proptosis, rapidly enlarging eyelid lesions, pigmentation changes, sentinel vessels, persistent unilateral inflammation, recurrent chalazion and atypical orbital imaging findings. These are not merely examination findings; they are clinical alarms. The first step in ocular oncology is often suspicion rather than treatment.

Residents should develop a basic understanding of common ocular tumors across age groups. In pediatric oncology, retinoblastoma, dermoid cysts, capillary hemangioma and rhabdomyosarcoma are essential entities. For adults, familiarity with choroidal melanoma, choroidal metastasis, conjunctival melanoma, ocular surface squamous neoplasia and eyelid malignancies such as basal cell carcinoma and sebaceous gland carcinoma is crucial. Orbital lesions including lymphoma, cavernous venous malformations and metastatic tumors also deserve attention. Residents are not expected to master the complexities of molecular oncology or advanced therapeutics during training, but they should understand the clinical presentation, differential diagnosis and urgency associated with these conditions.

Imaging also forms an important part of ocular oncology education. Modern ophthalmology increasingly depends on multimodal imaging, and oncology is no exception. In my recent orbital oncology lecture with residents, I was telling them that the most terrifying orbital lesion for a resident is – the radiologist calmly ending the report with "correlate clinically". Residents should appreciate the role of ultrasonography, optical coherence tomography, fundus autofluorescence,

Residency exposure to tumor boards or multidisciplinary discussions can help young ophthalmologists appreciate how collaborative modern cancer care has become.

They should acquire sufficient knowledge to identify suspicious lesions, perform an informed clinical evaluation, initiate appropriate investigations and refer patients without delay.

MRI and CT imaging in diagnosis and follow-up. Documentation through photography is equally critical, not only for monitoring progression but also for communication within multidisciplinary teams. Learning how to systematically document a lesion can significantly improve clinical reasoning.

Equally important is realising that ocular oncology is deeply multidisciplinary. The management of ocular tumors often involves pediatric oncologists, radiation oncologists, pathologists, neuroradiologists, and medical oncologists. Residency exposure to tumor boards or multidisciplinary discussions can help young ophthalmologists appreciate how collaborative modern cancer care has become. Ocular oncology, therefore, broadens a resident's perspective beyond the eye itself and reinforces the idea that ophthalmology is closely connected to systemic medicine.

How much should a resident know?

The answer lies in understanding the purpose of residency training. Residents are not expected to become ocular oncologists within three years. Instead, they should acquire sufficient knowledge to identify suspicious lesions, perform an informed clinical evaluation, initiate appropriate investigations and refer patients without delay. They should know when not to observe a lesion casually, when biopsy is necessary, and when urgent referral could change prognosis entirely.

In many ways, ocular oncology teaches humility. It reminds clinicians that not every lesion is benign and not every red eye is inflammatory. Residents learn to pause, think and correlate findings rather than relying solely on common diagnoses. This mindset benefits all aspects of ophthalmology practice.

The human aspect of oncology

Beyond academics and diagnostics, ocular oncology also carries a deeply human side. Discussions around cancer involve fear, uncertainty and emotional vulnerability. Counseling parents of a child with retinoblastoma or discussing the possibility of enucleation with a patient requires empathy and maturity. Residents exposed to ocular oncology often develop stronger communication skills because they learn that medicine is not only about disease management, but also about guiding patients through difficult decisions with honesty and compassion.

The future of ocular oncology

Fortunately, the field of ocular oncology is evolving rapidly. Advances in targeted therapy, intravitreal chemotherapy, proton beam therapy, molecular diagnostics and globe-salvaging procedures have dramatically improved outcomes over the last few decades. Conditions that once inevitably resulted in loss of the eye now often achieve both survival and useful vision. This progress makes the field intellectually exciting and reinforces the importance of early diagnosis.

Ultimately, ocular oncology for residents is not about memorizing every tumor classification or treatment protocol. It is about developing awareness, clinical suspicion and responsibility. The eye may be small, but the diseases affecting it can have enormous consequences. A resident who recognizes an ocular tumor early may save not only sight, but a human life itself.

Awards fade, titles evolve and achievements pass with time. Deep within the most meaningful and more fulfilling moments are when a young fellow walks upto me and says, "You inspired me to choose Ocular Oncology during my residency." Because in that moment, you realize that beyond treating tumors, you may have helped shape the future of the specialty itself and ignited a passion.

Ollie Saves Neo: *The Roar That Chose Love Over Pride*

ROLIKA BANSAL
SANTOSH G. HONAVAR

Dr. Rolika Bansal
has established the Division of Ocular Oncology and Oculoplasty at Mahatma Gandhi Hospital Jaipur, Rajasthan. She has been trained in Oculoplasty and Ocular Oncology under the guidance of Dr. Santosh Honavar (Centre for Sight, Hyderabad, India), Dr. Carol L. Shields (Wills Eye Hospital, Philadelphia, USA), Dr. Don O. Kikkawa and Dr. Bobby S. Korn (Shiley Eye Institute, San Diego, USA). Her work on over 110 research projects has resulted in >85 indexed and non-indexed publications, development of psychology-based programs for patients and a series on the legendary lives of "Women in Ophthalmology". Her awards include the coveted Col. Rangachari Award (AIOS), Lanna Cheng Innovation Award, Joanne Angle Award (Women in Ophthalmology), Retina Research Foundation Helmerich Award (IOFF). Additionally, she enjoys reading, writing, traveling, dancing, singing, painting and photography, and is grateful for her mentors' lifetime guidance.

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"Ollie" is the official Retinoblastoma Awareness Mascot of the Retinoblastoma Foundation, India. A wide-eyed, bow-wearing tiny owlet with a big mission: To make sure no child in the animal kingdom loses sight or life to retinoblastoma from lack of awareness.

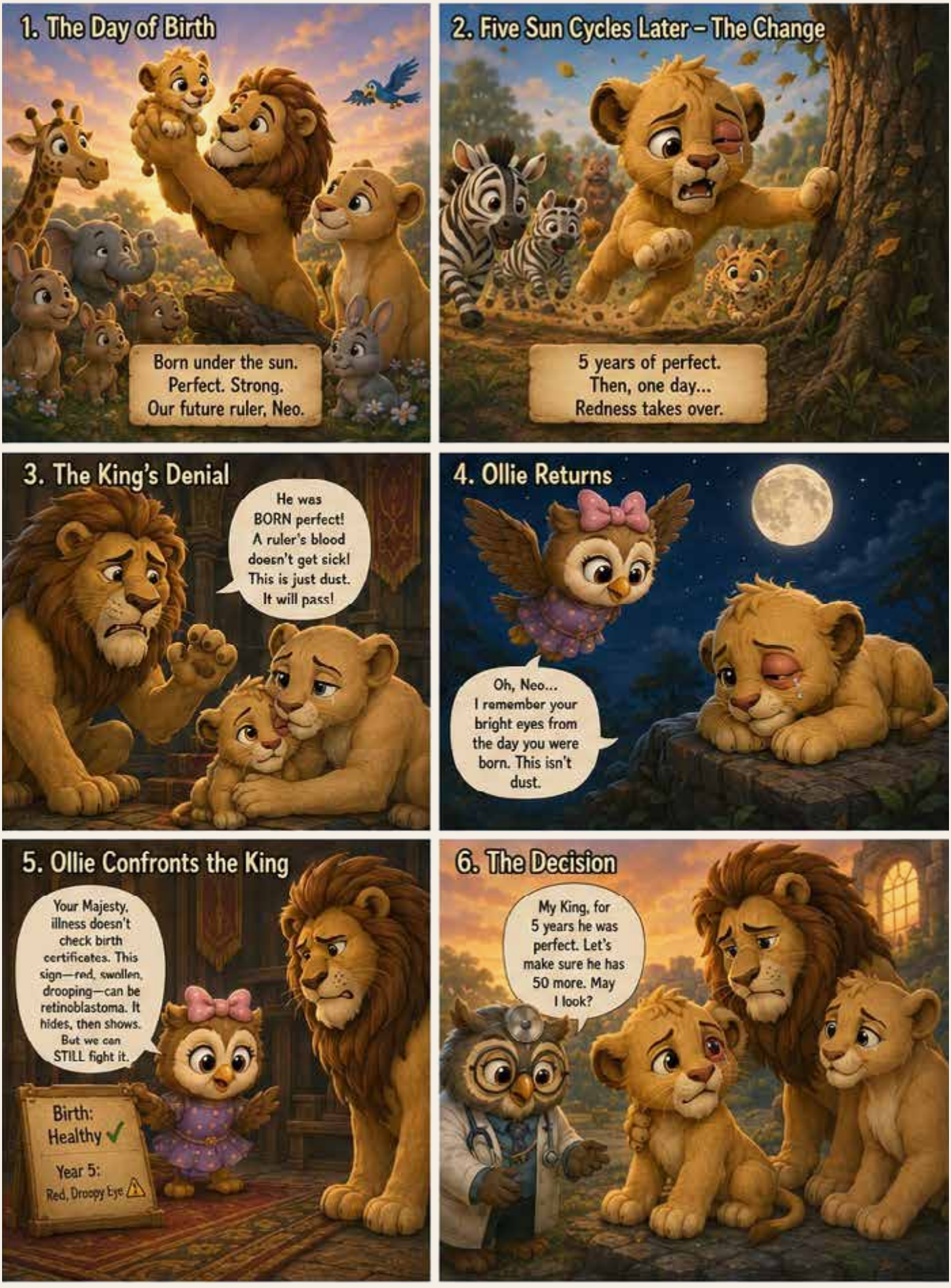
Ollie was designed as a clinical messenger in disguise. She was the first to be diagnosed with retinoblastoma in the animal kingdom at the age of 2-years when her mom-owl clicked a picture of her eye in the firefly flash camera and dad-owl noticed an abnormal white reflex in Ollie's eye. They took her in time to Dr. Hoot and she was treated promptly, thus leading to vision, eye and life salvage.

Since then, Ollie flies across the animal kingdom to help young animals and their families recognize the signs of retinoblastoma ranging from leukocoria, squint, vision changes redness, to proptosis. Each story ends with Ollie guiding them to Dr. Hoot, the kind specialist owl, reinforcing the core message - to see a doctor, early, without fear.

Ollie's adventures normalize real aspects of treatment ranging from chemotherapy, focal treatment, enucleation and multimodal management to living confidently with a prosthetic eye, showing children and parents that retinoblastoma is treatable, survival is possible, and life after retinoblastoma can still be royal, brave, and beautiful.

With retinoblastoma curable in >95% of cases when caught early, awareness is the most powerful drug we have. Ollie translates complex medical facts into love, courage, and action for families, while giving ocular oncologists, ophthalmologists and pediatricians a friendly, stigma-free tool for counseling.

From clinic walls to social media, classrooms to community camps, Ollie is here to "Fight the White", because every child deserves to see the moon, the stars, and their own bright future.



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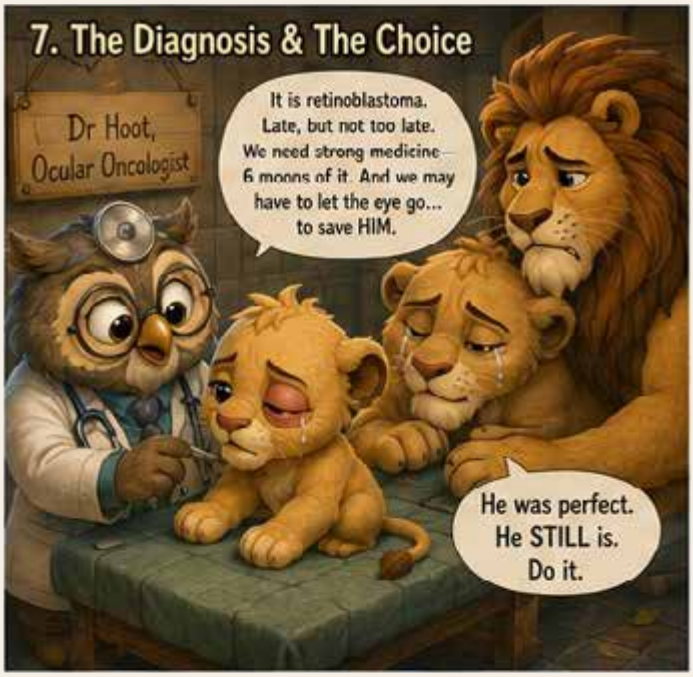
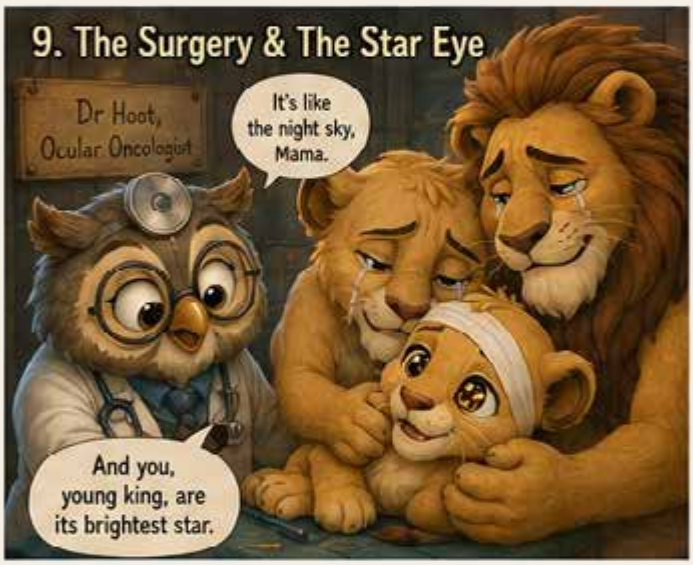

7. The Diagnosis & The Choice
Dr Hoot, Ocular Oncologist
It is retinoblastoma. Late, but not too late. We need strong medicine— 6 moons of it. And we may have to let the eye go... to save HIM.
He was perfect. He STILL is. Do it.


8. The Treatment Journey – 6 Cycles
Cycle 1
Cycle 3
Cycle 5
Cycle 6
6 moons. Not a prince being treated... a hero becoming one.


9. The Surgery & The Star Eye
Dr Hoot, Ocular Oncologist
It's like the night sky, Mama.
And you, young king, are its brightest star.


10. The Comeback
He sees with his heart now.


11. The New King


12. Ollie's Message to Parents
Rb can come late.
Cheers to every cub whose parents chose love over fear.

Eyedea
Innovator's Nook

FOCUSED, PIERCING, SHARP AND ABLAZE
A STIMULATED MIND OR A PREDATOR'S GAZE?

Ocular Oncology.

PURENDRA BHASIN
WHITE-EYED BUZZARD
PANNA
MADHYA PRADESH, INDIA

E-Moles - *A Deep Learning Algorithm to Aid in the Differentiation Between Benign and Malignant Melanocytic Choroidal Lesions*

ISABEL A. JOIA
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Imagine working as a community optometrist or ophthalmologist when a 56-year-old female patient walks into your office presenting with a small floater in her left eye, ongoing for several months. At first glance, this seems routine, likely vitreous opacities, a common finding in daily practice. As a diligent professional, you proceed with indirect ophthalmoscopy. While you do confirm vitreous opacities in the left eye and confidently rule out any retinal tear, your attention is drawn to an additional finding: a small dark spot located just temporally to the macula (Figure 1). Although you have encountered many choroidal nevi before, something feels slightly off about this lesion and you do wonder, does this lesion warrant referral to a specialist for further evaluation?

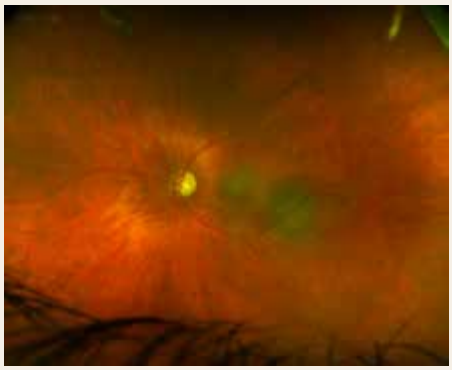

Figure 1: *56-year-old female patient with a choroidal melanocytic lesion temporally to the macula in the left eye*

The described scenario highlights a dilemma frequently encountered by non-specialists. Choroidal nevi are relatively common, with a prevalence of around 5%, although this varies widely across different populations.[1–4] Much like moles or freckles

on the skin, they are typically benign and harmless. However, distinguishing a nevus from a malignant melanoma is not always straightforward, as they can have very similar clinical presentations. Uveal melanoma is far rarer, with an incidence of approximately 5 cases per million, but it carries significant risk.[5–9] While primary choroidal melanomas can cause local tissue damage, the most serious concern is distant metastasis, most commonly to the liver, which is associated with a poor prognosis. Once metastasis has occurred, median overall survival is approximately 10–13 months with current systemic treatments.[10–12] More broadly, a diagnosis of uveal melanoma carries an estimated 50% risk of developing metastatic disease and an overall 10-year survival rate of about 43%.[13,14]

Accurate and timely diagnosis of choroidal melanoma is therefore critical. It is however important to consider that benign nevi outnumber choroidal melanomas by an approximate ratio of 9000 to 1. Referring every melanocytic lesion for further evaluation would significantly burden both patients and the healthcare system. Clinical assessment tools using mnemonics have, therefore, been developed to aid general ophthalmologists safely assess such lesions using TFSOM-DIM, which requires specialist imaging such as B scan ultrasound.[15] More recently, the MOLES scoring system has been developed to guide optometrists and non-specialists when considering whether to refer patients for a specialist opinion.[16] MOLES evaluates five key features: **M**ushroom shape, **O**range pigment, **L**arge size, **E**nlargement and **S**ubretinal fluid. Each feature is scored from 0 to 2, generating a total score that guides clinical management.

Table 1: *MOLES scoring system*

Category	Score	Description
Mushroom shape	0 1 2	Absent Unsure Present
Orange pigment	0 1 2	Absent Unsure/trace Confluent clumps
Large size	0 1 2	Thickness < 1.0 mm and 3 disc diameters in LBD (largest basal diameter) Thickness 1.0 – 2.0mm and/or 3 – 4 disc diameters in LBD Thickness > 2.0 mm and/or > 4 disc diameters in LBD
Enlargement	0 1 2	None (or lesion not documented or mentioned to patient previously) Unsure (i.e. poor image quality) Definite (confirmed with sequential imaging)
Subretinal fluid	0 1 2	No subretinal fluid Trace (if minimal and detected only with OCT) Definite (if seen without OCT)

Table 2: *Clinical management*

Total MOLES score	Definition	Clinical outcome
0	Naevus	Monitor in community
1 - 2	Indeterminate	Referral to General Ophthalmologist
>2	Likely choroidal melanoma	Urgent referral to Ocular Oncologist

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While MOLES has great clinical value and has been validated through numerous studies, the use of artificial intelligence (AI) for the diagnosis of retinal pathologies has been intensively investigated with the goal of automating the triaging and diagnostic process.[16-20] Currently, it is known that for a number of ocular conditions, AI can match and even exceed the diagnostic accuracy of experts and recently developed deep learning algorithms for a number of ocular pathologies have achieved regulatory approvals by the US Food and Drug Administration and European Union Medical Device Regulation.[21–23]

A fundamental requirement for developing robust and reliable medical AI models is access to large, high-quality datasets. In ocular oncology, progress in deep-learning models has been constrained by the relative scarcity of cases and the limited number of available imaging data. To overcome this, we have compiled over a decade of imaging data from patients attending Moorfields Eye Hospital, London, UK, a national referral centre for suspicious melanocytic lesions. Building on an extensive dataset of choroidal nevi and melanomas, we are developing a deep learning model, e-MOLES, designed to automate MOLES scoring. The model requires only a high-quality fundus image as an input and outputs a corresponding MOLES score. Preliminary iterations of our model have demonstrated a diagnostic accuracy exceeding 95% and further optimization and validation of e-MOLES are underway.

The clinical implementation of e-MOLES has the potential to significantly improve patient care. By supporting non-specialists in making safe and timely decisions, e-MOLES reduces the number of unnecessary referrals to the few specialist ocular oncology centres. In addition, the model produces an interpretable output that aligns with the established MOLES criteria, enabling users to understand and verify the basis of each classification. This transparency enhances clinical trust and facilitates integration of e-MOLES into practice. Ultimately, the clinical implementation of e-MOLES means that only the most serious cases will be referred to specialist centres, revolutionizing ocular oncology pathways for early diagnosis and treatment for patients.

Returning to our introductory example, you take an image of the small dark spot located just temporally to the macula, the e-MOLES score is automatically calculated and pops up on your screen: 0-2-0-0-2. On closer inspection, the presence of clumps of orange pigment and subtle washed-out appearance along the inferior margins of the lesion, suggestive of subretinal fluid, corroborates the model's assessment. Reassured you are making the right decision, you refer the patient to an ocular oncologist.

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Conflicts of interest

There are no conflicts of interest

Presented at

Retina Society 2023

Patent

No

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The Living Library for Uveal Melanoma: *A Patient-derived Organoid Biobank*

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Uveal melanoma is the most common primary intraocular cancer in adults. As an ocular oncologist, this is one of the most common conditions I diagnose and treat. Unfortunately, most eyes require treatment with high dose radiation, which often causes irreversible vision loss, and despite effective treatments for the eye tumor, about half of patients will still develop metastatic spread of cancer outside the eye. Giving the news that cancer has spread is one of the hardest parts of my job, especially because there are very limited treatment options for metastatic uveal melanoma. As a result, from very early in my career, I have felt compelled to contribute to research that will support more effective treatments for patients affected by this disease.

A major challenge of laboratory research in uveal melanoma has been a lack of disease models that accurately represent the human condition. Many times, there have been promising responses to drugs tested in the laboratory, but the treatments are ultimately unsuccessful in human clinical trials. These historical shortcomings have suggested that traditional laboratory models of uveal melanoma may give falsely optimistic drug response results that do not accurately represent what we see in our patients. Thus, our team sought to create improved models that would more accurately represent clinically relevant features and behavior of human uveal melanoma.

I first learned about organoids from my colleagues in medical oncology. Patient-derived organoids are three-dimensional tumor models generated directly from the tumor tissue of an affected patient. These models are an important bridge between two-dimensional cell line models and more expensive and time-consuming animal models. Compared to two-dimensional cell lines, organoids may better represent tumor behavior in live patients.

At our hospital, a pancreatic cancer researcher had generated three-dimensional tiny tumors from pancreatic cancer tissue, and his group was able to show that the organoid response to treatment in the laboratory mirrored the treatment response of patients in clinic who had donated the corresponding tumor tissue. Hoping that we could apply this type of model to uveal melanoma, I sought to learn the technique from my colleagues. Our first attempt to generate patient-derived organoids from uveal

melanoma utilized tumor tissue from an eye that had to be removed due to a large tumor. While we were able to successfully generate organoids, the growth on our initial attempt was limited. We had used a large dish for growth, following the protocol that our colleagues had previously used to generate organoids from a larger pancreatic cancer sample. We surmised that given the smaller size of eye tumors, we needed to scale down our organoid production into a smaller dish. Once doing so, we noticed improved growth of our organoid models.

Excited with this early success, we sought to grow a biobank of organoid models from a diverse range of patients with different subtypes of uveal melanoma. (Figure 1) We generated additional organoids from eye tumors both in our center and in other centers in the United States, and we further expanded to generate organoids from metastatic uveal melanoma tumors. Once we had developed multiple unique organoid models, we sought to better characterize how well these organoids represented the tumors from which they had been generated.

Multiple features were important to characterize when considering how representative our models were of human disease. First, we confirmed that we indeed had melanoma cells by using immunostaining for melanoma-specific markers, and we examined the organoids under the microscope to confirm melanoma morphology of the cells. Then, we checked tumor-specific mutations to see if each individual organoid had mutations matching the primary donor tumor. After confirming these core features, we checked gene expression profiles of the organoids and found a variety of gene expression profiles matching different uveal melanoma subtypes that have been seen in human tumors. Because the organoids can be grown as a renewable resource, we also assessed some exploratory sequencing tests to try to identify new targets for uveal melanoma treatment.

Next came the daunting task of determining whether these organoid models better represent uveal melanoma drug response. A major challenge with validating the models' drug response is the lack of effective uveal melanoma treatments. We unfortunately lack a drug that is highly effective for uveal melanoma, so it remains difficult to prove that our organoids would have a good response to an effective treatment. We used a drug in clinical trial with some promising results as a surrogate positive control treatment along with several drugs that had previously shown promising laboratory results but failed to improve outcomes in clinical trials. We compared the response of our organoid models to traditional two-dimensional cell line models. We found that our models better represented the treatment resistance seen in clinical trials unlike traditional cell line models that showed falsely optimistic treatment response. We saw variable responses to the clinical trial drug, with some organoids showing good response. Overall, our early results suggest that our models may better represent drug responses for distinct uveal melanoma subtypes seen in the clinic.

We continue to grow the biobank, which contains more than 50 unique uveal melanoma organoid models from both primary eye and secondary metastatic tumors, and we continue to accept tumor tissue from centers throughout the United States to expand the diversity of the tumors in our library. We are using these models to uncover unique targets that might help better treat this type of cancer, and we are also testing novel combination therapies to overcome treatment resistance. We are sharing these models for collaborative work to provide a better benchmark for uveal melanoma treatment response in the laboratory,

ultimately aiming to support improved translation of promising laboratory results to the clinic. Our hope is that these models will form the foundation for development of more effective strategies to improve quality and quantity of life for patients affected by uveal melanoma. We are grateful to our patients who have donated tumor tissue for the biobank, and we look forward to a brighter future, with more effective treatments for the uveal melanoma community.

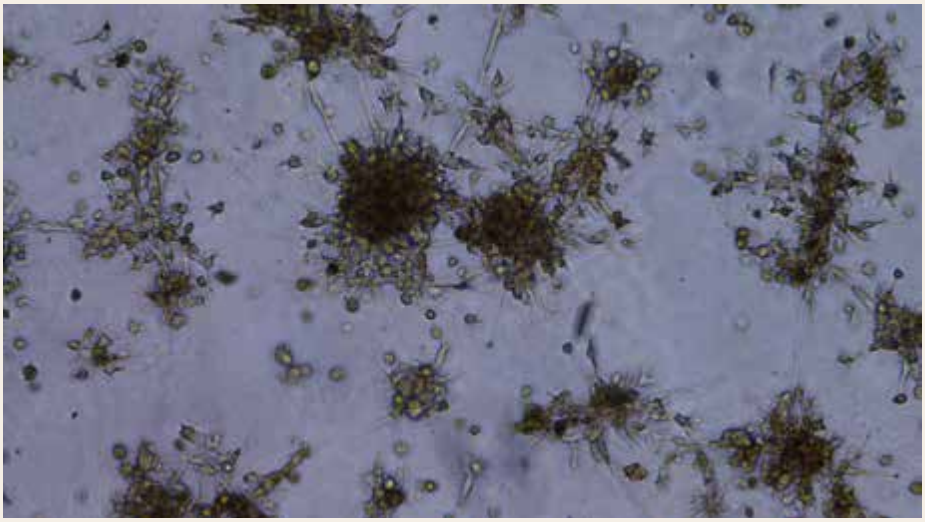

Figure 1: *Uveal melanoma patient-derived organoid*

Presented at

ISOO, APAO, ARVO

Best Paper Award at ISOO 2024

Patent

No

Suggested reading

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Aqueous Humor Liquid Biopsy in Vitreoretinal Lymphoma- *A Novel Option for Monitoring and Follow-up*

HAKAN DEMIRCI

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Vitreoretinal lymphoma can mimic other intraocular disorders, including inflammatory and neoplastic conditions, and may even be subclinical, making both diagnosis and longitudinal follow-up challenging. Currently, the diagnosis of vitreoretinal lymphoma relies on clinical examination combined with multimodal imaging and cytopathologic analysis of specimens obtained via pars plana vitrectomy. Similarly, surveillance for recurrence depends on clinical examination and imaging. However, both clinical assessment and existing imaging modalities have inherent limitations, and the characteristically low cellular yield of vitreous samples frequently hinders definitive cytopathologic diagnosis. Given these challenges, there is a clear need for improved diagnostic and monitoring tools for vitreoretinal lymphoma.

In central nervous system (CNS) diffuse large B-cell lymphoma (DLBCL), the most frequently mutated genes include MYD88, PIM1, and KMT2D. MYD88 is an adaptor protein that links Toll-like receptor to critical downstream intracellular signaling pathways.[1] The L265P gain-of-function mutation involves leucine to proline amino acid substitution at 265 codon affecting the MYD88 Toll/IL-1 receptor (TIR) domain. MYD88 L265P gain-of-function mutation leads to assembly of protein complex containing IRAK1 and IRAK4. This leads to oncogenic signaling cascades in DLBCL. The MYD88 L265P mutation is detected more frequently in DLBCL arising at immune-privileged sites than at other anatomic locations, with reported prevalences of 60% (95% CI: 42.2–75.2%) in CNS lymphomas and 77.1% (95% CI: 67.1–84.7%) in testicular lymphomas. In vitreoretinal lymphoma specifically, the MYD88 L265P mutation has been detected in up to 88% of patients. More recently, this mutation has been identified in the aqueous humor of vitreoretinal lymphoma patients in up to 89% of cases.

Based on these findings, we began analyzing aqueous humor as a potential substrate for a less invasive diagnostic and monitoring test for vitreoretinal lymphoma. Aqueous humor can be readily obtained in an outpatient setting via anterior chamber paracentesis, potentially obviating the need for vitrectomy-based approaches that require specialized equipment, an operating theater, and carry procedural risks—particularly relevant for patients who may be systemically debilitated by lymphoma. Detection of the MYD88 L265P mutation in aqueous humor may, therefore, serve as a surrogate, minimally invasive biomarker for both diagnosis and longitudinal monitoring.

We investigated whether the MYD88 L265P mutation could be detected in aqueous humor using a simple allele-specific real-time polymerase chain reaction (AS-qPCR) assay, and whether serial measurements could be used to monitor treatment response. We found that the MYD88 L265P mutation was detectable in 83% of patients with biopsy-confirmed or clinically diagnosed vitreoretinal lymphoma when both cellular and cell-free DNA (cfDNA) were analyzed. Notably, the inclusion of cfDNA enabled detection of the mutation in an additional one-third of positive cases that would otherwise have been missed using cellular DNA alone.

We further explored the utility of serial aqueous humor MYD88 L265P mutation testing for monitoring treatment response. Determining the optimal duration of intravitreal chemotherapy or assessing whether systemic chemotherapy has adequately eradicated intraocular disease remains a significant clinical challenge. In our initial experience, the MYD88 L265P mutation converted from detectable to undetectable in the aqueous humor of up to 90% of patients following three cycles of combined intravitreal methotrexate and rituximab injections. Among these patients, no recurrences were observed up to a follow-up of 13 months. In contrast, the mutation remained detectable in 10% of patients after completion of intravitreal therapy, and these patients' developed recurrence of vitreoretinal lymphoma within 6 months of completing treatment.

We are currently expanding this cohort with additional patients and longer follow-up, and preliminary results are consistent with our initial findings.

In summary, our results demonstrate that detection of the MYD88 L265P mutation in aqueous humor can serve as a minimally invasive surrogate biomarker for the diagnosis of vitreoretinal lymphoma, as well as for surveillance and monitoring of treatment response. A simple anterior chamber paracentesis to obtain aqueous humor may represent a practical alternative to vitreous biopsy, reducing procedural burden, time, and resource utilization while providing clinically actionable molecular information.

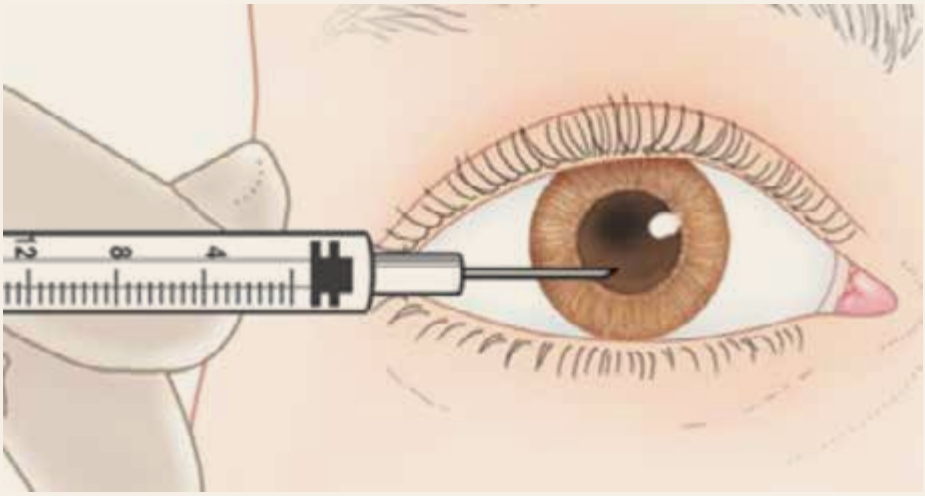

Figure 1: *Anterior chamber paracentesis for the collection of aqueous humor*

Figure 2: *Fundus, autofluorescence and OCT images of vitreoretinal lymphoma*

Declaration of patient consent

The author certifies that all the appropriate patient consent has been obtained for publication for scientific purposes.

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Eyedvantage

BE ALERT, ABREAST AND AWARE
IT'S A JUNGLE OUT THERE!

A brief review of interesting developments in ophthalmic sub-speciality.

ADITYA KELKAR

TIGRESS WITH HER KILL, SAMBAR DEER
RANTHAMBORE
RAJASTHAN, INDIA

Intra-operative Cytological Diagnosis: *The Unsung Maestro of the Operating Theatre*

A Clinical Education Monograph from the Ophthalmic Pathologist

KAUSTUBH MULAY

Dr. Kaustubh Mulay
heads the National Reporting Centre for Ophthalmic Pathology at Centre for Sight, Hyderabad. He has published in several peer-reviewed journals and has many presentations and posters to his credit, both, national and international. Some of his major awards and honours include the Dr. Gangadhar Sundar Gold Medal at OPAI, Dr. S.C. Dutta Award at AIOS, G.Subbalaxmi Gold Medal for Young Scientist and several other best paper awards at the AIOS and IAPM meetings.

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In the operating room, decisions often cannot wait. Margins must be cleared, tumor nature clarified, and surgical plans adapted, sometimes within minutes. In over two decades of examining the specimens of patients who could not afford to lose another cubic millimetre of tumour to a diagnostic cryostat, I have returned again and again to a technique that demands neither refrigerant nor sophisticated machinery — only a clean glass slide, a practiced hand, and an inquiring mind. Intra-operative cytological diagnosis is not new; it is not fashionable; and it is emphatically not second best. It is, in the right hands and the right circumstances, the single most elegant tool available to the ophthalmic pathologist serving a surgeon who needs an answer 'now'.

This monograph is my attempt to place that tool in your hands, and to persuade you, with evidence, that it belongs there.

What is intra-operative cytological diagnosis (IOCD)?

At its most elemental, IOCD is the rapid microscopic examination of cells procured from a fresh surgical specimen while the patient remains on the operating table and the surgeon awaits guidance. Unlike conventional histopathology — which examines architecture, stroma, and spatial relationships between cells — cytology concerns itself with the cell itself: its nucleus, its chromatin, its cytoplasm, its companions.

The governing principle is deceptively simple: cellular morphology alone can, in most ophthalmic tumors, distinguish

Intra-operative cytological diagnosis is not new; it is not fashionable; and it is emphatically not second best. It is, in the right hands and the right circumstances, the single most elegant tool available to the ophthalmic pathologist serving a surgeon who needs an answer 'now'.

The squash smear is the great equalizer: it costs nothing, requires nothing, and reveals everything the nucleus wishes to confide.

malignant from benign, primary from metastatic, epithelial from mesenchymal, and lymphoid from non-lymphoid.

In the operating theatre, where a biopsy from an orbital apex may yield barely a fragment visible to the naked eye, or where an intraocular mass must be characterized without sacrificing the globe, this philosophy is not merely convenient — it is transformative.

The pathologist's palette: Techniques of specimen preparation

Intra-operative cytology is not a single manoeuvre. It is a repertoire — and the skilled pathologist selects from it as a musician selects from an instrument. Each technique has its strengths, its limitations, and its ideal application.

- **Touch imprint (impression) cytology**

The cut surface of fresh tissue is gently pressed against a glass slide, transferring the outermost layer of exfoliated cells. Simple, rapid, and crucially, non-destructive. The surgeon's specimen emerges intact for permanent sectioning, and the pathologist has a cellular map of the cut margin. In orbital biopsies and conjunctival lesions, imprint cytology provides an immediate, high-fidelity cellular portrait.

- **Squash (crush) smear**

A small fragment of tissue is placed between two glass slides and compressed gently, spreading a monolayer of cells that is incomparable for cellular detail. Particularly revelatory for soft, friable lesions — retinoblastoma, lymphoma, metastatic carcinoma, and small round cell tumors of the orbit surrender their secrets beautifully to this technique. The squash smear is the great equalizer: it costs nothing, requires nothing, and reveals everything the nucleus wishes to confide.

- **Scrape cytology**

The cut surface of firmer tissues is scraped gently with a blade or the edge of another slide, and the harvested material is smeared. Useful when imprint yields scant cellularity — as may occur with fibrous or desmoplastic tumors — scrape cytology should be considered a complementary manoeuvre rather than a default.

- **Intra-operative fine needle aspiration**

For deep-seated or anatomically inaccessible lesions — a posterior orbital mass, a suspected uveal melanoma approached through a transcleral route — fine needle aspiration cytology, performed intra-operatively, provides material for immediate smear examination. Here, cytology and surgery converge in real time.

— ***A note on staining***

Rapid stains — Diff-Quik for air-dried smears, or ultrafast Haematoxylin and Eosin and modified Papanicolaou (PAP) for alcohol-fixed preparations — reliably deliver stained slides within 5 to 15 minutes. Turnaround time (TAT) from specimen receipt to verbal report can, in an experienced laboratory, be fewer than ten minutes. No cryostat. No technician skilled in frozen section. Just slides, stain, and knowledge.

Frozen section and cytologic smear: Allies, not rivals

The frozen section has dominated intra-operative diagnosis for over a century — and it has earned that dominance. But it is time to examine the claim with the dispassionate eye of a scientist rather than the reverence of tradition.

Cytology sacrifices architecture but, in doing so, eliminates the freezing artefact — that bane of the frozen-section enthusiast which distorts nuclear chromatin, creates ice-crystal vacuoles, and may transform a clearly malignant nucleus into an ambiguous one.

In this context, the principle that cytology consumes a single cell layer while frozen section consumes a 5-micron slice — multiplied by the multiple levels typically cut — is not academic. It is the difference between a diagnosis and a histopathological blank.

Table: *Comparision of intraoperative cytology and frozen section*

Feature	Intra-operative Cytology	Frozen Section	Advantage
Sample basis	Individual cells	Tissue architecture	Cytology
Processing	Smear-based	Cryostat sectioning	Cytology
Turnaround time	5–15 minutes	15–30 minutes	Cytology
Tissue consumption	Minimal	Significant	Cytology
Freezing artifact	None	Common	Cytology
Cellular detail	Superior	Moderate	Cytology
Architectural info	Limited	Excellent	Frozen Section
Infrastructure	Minimal	Cryostat required	Cytology
Cost	Low	Higher	Cytology

The fundamental distinction is this: frozen section preserves the architectural relationships between cells and stroma, permitting assessment of invasion, pattern, and grade. Cytology sacrifices architecture but, in doing so, eliminates the freezing artefact — that bane of the frozen-section enthusiast which distorts nuclear chromatin, creates ice-crystal vacuoles, and may transform a clearly malignant nucleus into an ambiguous one.

For ophthalmic specimens — where tissue is measured in milligrams, not grams — this is not a trivial exchange. Every tissue section cut on a cryostat is tissue irretrievably consumed and unavailable for the permanent section, immunohistochemistry, or molecular studies that may determine not merely diagnosis but prognosis and treatment.

"In ophthalmic oncology, where every micron of tissue is irreplaceable currency, the cytological smear is not an economy — it is an investment."

The case for cytology: Evidence-based advantages

- **Superior cellular morphology**

The absence of freezing artefact is not merely aesthetic. In the small round blue cell tumours that populate paediatric ophthalmic oncology — retinoblastoma, rhabdomyosarcoma, Ewing's sarcoma, lymphoma — nuclear chromatin pattern, nucleolar prominence, and mitotic morphology are decisive diagnostic features. The squash smear preserves these features with a fidelity that the frozen section, however expertly prepared, cannot consistently match.

- **Tissue conservation — the ophthalmic imperative**

No other surgical specialty confronts the pathologist with the relentless tissue economy of ophthalmic surgery. An orbital biopsy may yield 3 millimetres of tissue. An intraocular aspirate may yield 0.2 millilitres of vitreous. In this context,

Cytology cannot assess invasion, depth of invasion, perineural spread, vascular involvement, or stromal reaction.

the principle that cytology consumes a single cell layer while frozen section consumes a 5-micron slice — multiplied by the multiple levels typically cut — is not academic. It is the difference between a diagnosis and a histopathological blank.

- **Speed and accessibility**

In resource-limited settings, the absence of a cryostat is not a deficiency to be apologized for; it is an opportunity for cytology to assert its primacy. The technique requires a clean glass slide, a staining jar, and a microscope. In community hospitals, district-level cancer centres, and indeed in any operating theatre where frozen section infrastructure is unavailable, the cytological smear offers diagnostic capability that would otherwise be absent entirely.

- **Diagnostic accuracy: What the literature tells us**

The evidence, when examined carefully and restricted to properly designed studies, is compelling:

— Vemuganti et al. reporting from the L.V. Prasad Eye Institute, Hyderabad, evaluated squash and imprint cytology in 45 consecutive ocular and orbital specimens.[1] Adequate cellularity was obtained in all cases. The authors concluded that these techniques provide rapid and reliable intra-operative diagnosis, assuming the availability of a skilled cytologist or ophthalmic pathologist.

— Font, Lazcano and Ramzy studied 84 orbital and ocular adnexal tumours using the squash technique and demonstrated its reliability across a wide spectrum of tumour types, cementing its role in ophthalmic pathology practice.[2]

— In a study of intra-operative cytology across multiple organ systems, diagnostic accuracy of the imprint technique for differentiating benign from malignant lesions reached 100% in solid organ specimens, with an overall accuracy of 92.7% for lymph nodes.[3]

— A landmark comparative study of CNS lymphoma demonstrated that frozen section alone achieved diagnostic accuracy of 77–79%, whereas combining frozen section with intra-operative cytology raised accuracy to 86–87%, and the addition of rapid immunocytochemistry elevated it further to 92.7%.[4]

— For impression cytology in ocular surface neoplasia, a study comparing cytology with histology as the gold standard reported a positive predictive accuracy of 97.4%, supporting its role as a powerful screening and intra-operative tool.[5]

Honest counsel: The limitations of cytology

I have spent a career being direct with clinicians, and I will not abandon that habit in the service of advocacy. Intra-operative cytology has genuine limitations, and the thoughtful pathologist must own them.

- **Loss of architecture**

Cytology cannot assess invasion, depth of invasion, perineural spread, vascular involvement, or stromal reaction. In tumors where diagnosis depends on invasion (eg: intra-epithelial squamous neoplasia vs. squamous cell carcinoma or intra-epithelial conjunctival melanocytic lesions vs. melanoma), for tumors in which grading or margin-depth assessment is critical — basal cell carcinoma, certain lacrimal gland carcinomas, sebaceous carcinomas with pagetoid spread — the frozen section provides irreplaceable architectural information.

In the assessment of sentinel lymph nodes — particularly relevant in conjunctival melanoma and sebaceous carcinoma — frozen section has demonstrated superiority to cytology for the detection of micrometastatic deposits.

- **Sampling error**

The imprint reflects only the topmost cell layer of the cut surface. A tumour with a central necrotic core and viable peripheral cells may yield an imprint that is non-representative. The squash smear, which draws from a small tissue fragment, is similarly subject to the vagaries of sampling.

- **Operator dependence**

The technique is only as reliable as the pathologist interpreting it. The learning curve for cytomorphological diagnosis is steep. A trainee who can read a frozen section adequately may misinterpret a cytological smear disastrously. Supervision, mentorship, and systematic training are not optional — they are obligatory.

- **Micrometastasis detection**

In the assessment of sentinel lymph nodes — particularly relevant in conjunctival melanoma and sebaceous carcinoma — frozen section has demonstrated superiority to cytology for the detection of micrometastatic deposits. Cytology may miss isolated tumour cells or small clusters that a deeper cryostat level would reveal.

Intra-operative cytology in ophthalmic oncology: Tumour by tumour

Let us now descend from principle to practice — the only level at which pathology has any meaning.

In ophthalmic practice, intra-operative cytology is not just an alternative, it is often the more practical tool.

- **Ocular surface tumors**
  - —OSSN vs. benign lesions.
  - —Margin assessment via imprint cytology.
- **Retinoblastoma**
  - —Cytology provides rapid confirmation.
  - —Avoids excessive tissue handling.
- **Uveal melanoma**
  - —Helps differentiate melanoma vs. metastasis vs. lymphoma.
  - —Preserves tissue for molecular prognostication.
- **Orbital tumors**
  - —Small biopsies benefit from cytology-first approach.
  - —Useful in lymphoma, metastasis, inflammatory lesions.
  - —Can guide clinicians to conservative management and avoid unnecessary surgeries (eg: Eosinophilic granuloma).
- **Lacrimal gland lesions**
  - —Helps distinguish epithelial vs. lymphoid pathology intra-operatively.
- **Margin assessment**
  - —Imprint cytology allows ‘evaluation of entire cut surface’, unlike frozen section which samples selected areas.[6]

Can cytology replace frozen section? The considered answer

I am occasionally asked this question by trainees, and I confess that I find it the wrong question entirely.

The short answer: Not entirely—but it does not need to.

For those of us who have spent our careers in the service of the ophthalmic surgeon and the ophthalmic patient, intra-operative cytology represents something rather more than a technique. It represents a philosophy: that the most elegant diagnostic answer is usually the one that consumes the least, reveals the most, and arrives when it is needed.

- **The reality**
  - — Cytology is faster, simpler, and tissue-sparing.
  - — Frozen section provides architectural confirmation.
- **The ideal approach**
  - — Think of them as 'complementary tools, not competitors'.
  - — Evidence supports this combined approach.
  - — Using both methods improves overall diagnostic accuracy significantly.

The literature supports a combined approach as the diagnostic gold standard. The Scientific Reports 2024 CNS lymphoma study is instructive: frozen section alone, 77%; frozen section plus cytology, 87%; frozen section plus cytology plus rapid immunocytochemistry, 93%. Each modality adds diagnostic power that the others lack.[7,8]

The more useful question — the clinically productive question — is this:

"For this specimen, in this patient, at this moment in the procedure, which tool best answers the question the surgeon is asking?"

A practical decision framework

- **Deploy cytology when**
  - — Tissue is precious and must be conserved for permanent section, IHC, or molecular studies.
  - — Speed is paramount and cellular morphology is sufficient for the clinical question.
  - — A cryostat is unavailable or the specimen is unsuitable for freezing (e.g., calcified).
  - — Margin survey of an entire excised surface is required.
- **Deploy frozen section when**
  - — Tissue architecture and invasion patterns are diagnostically critical.
  - — Micrometastasis detection in sentinel nodes is the primary objective.
  - — Tumor grading or margin depth assessment will influence immediate surgical planning.
- **Deploy both when:**
  - — Diagnostic uncertainty is high and the surgical decision carries high stakes.
  - — You need both cellular confirmation AND architectural assessment for a confident diagnosis.

A final word

The history of pathology is, in large part, the history of new techniques displacing old assumptions. The stethoscope did not replace the hand; the CT scanner did not replace clinical examination; the frozen section need not — and should not — be replaced by cytology. But it must be joined by it.

For those of us who have spent our careers in the service of the ophthalmic surgeon and the ophthalmic patient, intra-operative cytology represents something rather more than a technique. It represents a philosophy: that the most elegant diagnostic answer is usually the one that consumes the least, reveals the most, and arrives when it is needed.

In ophthalmology, where the organ is small, the tumors are rare, the tissue is irreplaceable, and the stakes are high, that philosophy is not an option. It is an obligation.

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OCULAR ONCOLOGY

Retinoblastoma in 2026: *What's New at the Frontier?*

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Treatment of Retinoblastoma (RB) has been among the greatest success stories in ocular oncology, evolving till date. While established tools like intra-arterial chemotherapy (IAC), systemic chemotherapy (IVC), intravitreal chemotherapy and episcleral plaque brachytherapy have dramatically improved the life salvage and globe salvage rates, the field continues to progress . This article lists some of the latest advances such as AI-powered diagnostics to drug delivery systems and immunotherapy that are reshaping the discipline.

Emerging screening modalities

The single greatest determinant of outcome in RB remains the age at diagnosis. The earlier the diagnosis, the better is the prognosis. The two developments that deserve attention are prenatal diagnosis and AI-powered screening.

- **Genetic screening in RB**

The American Association of Cancer Research 2025 guidelines recommend germline RB1 testing for every child with RB, unilateral or bilateral, since any child can carry a de novo mutation. The shift from laborious sequential Sanger sequencing to NGS-based panel testing has been the engine of change: a single run now detects point mutations, copy number changes, and mosaicism down to a 2.5% allele frequency and the detection rates in bilateral probands accurately upto 96% as of July 2025.

The testing circle extends beyond the proband to both parents (even unaffected, given a 5% mosaicism risk), siblings, and

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adult survivors now having children, each of whose offspring carries a ~45% risk of inheritance.

The cost is no longer a barrier as it once was. In India, NGS-based RB1 panel testing now costs approximately ₹20,000 (~$240 USD), and data from Sankara Nethralaya showed genetic screening to be 3.5 times cheaper per proband than conventional clinical surveillance, rising to a sixfold saving for a family with two at-risk siblings, a compelling argument in a country carrying the world's largest RB burden.

- **Pre-implantation genetic testing and embryo transfer**

Starting with genetic counselling, families with a known germline mutation can opt for preimplantation genetic testing (PGT-M via IVF) before conception, embryo biopsy at the 8 cell stage and thereby transfer of healthy embryos. This procedure is currently available in India as well. The non-invasive prenatal diagnosis (NIPD) from 8 weeks of gestation — a definitive test from maternal blood, chorionic villus sampling (11–14 weeks) and amniocentesis (15–18 weeks) are the other alternate methods to diagnose.

- **USG doppler with microvascular flow imaging**

Once a mutation-positive pregnancy is established, microvascular flow imaging, a novel enhanced Doppler technique, can now visualise tumour bed vasculature from as early as 32 weeks in utero, outperforming standard greyscale ultrasound. Even without a visible tumour, delivery at 36 weeks is recommended, since 30% of RB1 carriers will already harbour an occult vision-threatening tumour at birth below any scan's resolution.

A Toronto cohort confirmed that prenatal identification with planned early delivery produced better visual outcomes with less invasive treatment. The clock starts at birth: ophthalmic examination must occur within 24 hours, and treatment, including intra-arterial chemotherapy, now feasible in infants as young as 35 days, begins immediately if a tumour is found.[1-7]

- **AI and ML in RB screening**

The ArMOR project (Artificial Intelligence and Machine Learning in Ocular Oncology, Retinoblastoma), a collaborative effort between L.V. Prasad Eye Institute, Hyderabad and Wills Eye Hospital, Philadelphia, has developed and validated an AI model to detect and classify RB from fundus images with high accuracy (sensitivity 94%, specificity 98%) in a multiracial cohort.[8]

Separately, a team from Memorial Sloan Kettering Cancer Center published in early 2025 that machine learning applied to RetCam images could reliably distinguish true retinoblastoma from pseudo-retinoblastoma, a notoriously tricky clinical problem that continues to result in misdiagnosis rates of up to 10% in some countries.[9]

A deep learning algorithm (DLA-RB) trained on over 47,000 images from Beijing Tongren Hospital achieved 99.8% probability of successfully distinguishing active RB from normal fundus, a performance level that could meaningfully supplement screening programmes in resource-limited settings.[10]

Emerging diagnostics in RB

- **Molecular profile and liquid biopsy**

Direct tumour biopsy is not considered in RB due to the risk of extra-ocular spread. Now, the aqueous humour (AH) is regarded a rich source of cell-free tumour DNA (cfDNA). Studies from the Children's Hospital Los Angeles have demonstrated that copy number alterations (CNAs) in AH cfDNA, particularly 6p gain and focal

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MYCN amplification, along with tumour fraction, correlate prospectively with intraocular relapse, treatment response, and globe salvage. In a study of 26 eyes from 21 patients, pathogenic RB1 variants were identified in 25 of 26 AH samples, with ocular salvage achieved in 73.1% of eyes.[11]

They also launched LBSeq4Kids, a clinically validated liquid biopsy platform that combines low-passage whole genome sequencing (for CNAs) with a custom targeted sequencing panel (for sequence variants). This platform analyses cfDNA from AH, cerebrospinal fluid, and plasma simultaneously, positioning it as a powerful tool for both intraocular and metastatic disease monitoring.[12]

- **Molecular analysis and tumour prognostication**

DNA methylation signatures of RB have been characterised from AH samples, potentially enabling tumour classification and prognostication without the need for enucleation. NGS panels applied to AH from 76 patients (162 samples) have further validated the utility of this approach in routine clinical settings.[13,14]

Emerging therapeutics in RB

Treatment of RB has been traditionally centred on systemic chemotherapy, intra-arterial chemotherapy, and intravitreal injections. The boundaries have been expanded by several genuinely novel approaches.

- **Intracameral chemotherapy for aqueous seeding**

Intracameral injection of melphalan (or topotecan) directly into the anterior and posterior chambers has emerged as an effective treatment strategy. Long-term data from a retrospective study of 20 patients showed that aqueous seeding control was achieved initially in all cases, with sustained control in the majority, and at 5-year follow-up, a subset of patients remained disease-free with intact vision.[2]

- **The chemoplaque: Sustained drug delivery from the sclera**

The chemoplaque is a novel episcleral drug delivery device with a small reservoir glued to the sclera that slowly releases chemotherapy (topotecan) into the vitreous. This maintains therapeutic drug levels and repeated intravitreal injections are avoided. The STEP-RB phase I clinical trial from 2020 to 2024, explored its safety and the phase II trial narrowed 2 of these (0.6mg each) as the most safe and efficacious dose.[1,2]

- **Suprachoroidal (SC) route of topotecan delivery**

A single SC injection of topotecan (50 µg/0.05 ml) achieved a selective tissue distribution (retina/plasma, 1377.8), that was 23-fold higher than that of IAC (58.9) and more than 1000-fold higher than IVC (1.32) while still being non-toxic to the retinal cells.[15]

- **Tylectomy: Tumour surgery makes a comeback**

Tylectomy refers to surgical removal of intraocular tumours via pars plana vitrectomy with intraoperative chemotherapy. Earlier avoided due to seeding risk, it is now being cautiously revisited. Studies show improved ocular survival without compromising overall survival. It remains a selective option for chemotherapy-resistant cases in expert hands.[2,16]

- **VCN-01: The oncolytic virus that eats tumours**

VCN-01 is a genetically engineered oncolytic adenovirus designed to selectively replicate within tumour cells, degrade the stroma, enhance the penetration of chemotherapy, and simultaneously stimulate the immune system against the tumour. A Phase I trial at the Children's Hospital,

Copy number alterations (CNAs) in AH cfDNA, particularly 6p gain and focal MYCN amplification, along with tumour fraction, correlate prospectively with intraocular relapse, treatment response, and globe salvage.

GD2-directed CAR-T cell therapy and GD2 vaccines are also under active investigation. While these remain experimental, the biological rationale is compelling and clinical translation is anticipated in the near-to-medium term.

Barcelona, evaluated intravitreal VCN-01 in 9 children with RB refractory to conventional treatment. The results, as of April 2024, were encouraging: 4 patients had an unequivocal improvement in vitreous seed density, and enucleation was avoided in 3 patients. Toxicity was predominantly grade 1–2, and no dose-limiting toxicities were observed.[17]

- **rAAV2-RB1 gene therapy**

In this study, an RB gene therapy system was constructed using RB1 as the target and AAV as the delivery vehicle and a safety assessment was conducted. In vitro, rAAV2-RB1 was effectively expressed in patient-derived RB cells. In mice, intravitreal administration of rAAV2-RB1 in a population-based patient-derived xenograft trial induced limited tumor growth.[18]

- **Nanoparticle mediated gene therapy**

Non-viral nanoparticles (NPs) such as lipid-based nanoparticles, polymeric nanoparticles, gold nanoparticles have displayed improved gene delivery owing to their improved pharmacokinetics, leading to better absorption, distribution, metabolism, and excretion in the physiological environment compared to viral ones.[19]

- **Immunotherapy in RB**

Retinoblastoma cells overexpress the ganglioside antigen GD2 — the same target exploited by dinutuximab (anti-GD2 monoclonal antibody) in high-risk neuroblastoma. Preclinical studies have demonstrated that anti-GD2 and anti-B7-H3 antibodies can effectively kill RB cells in vitro. GD2-directed CAR-T cell therapy and GD2 vaccines are also under active investigation. While these remain experimental, the biological rationale is compelling and clinical translation is anticipated in the near-to-medium term.[2,20]

RB: What's ahead?

Retinoblastoma in 2026 stands at a genuinely exciting inflection point. Liquid biopsy is moving from research tool to clinical companion diagnostic. AI is beginning to bridge the gap in diagnosis between high-income and low-resource settings. Novel local drug delivery (chemoplaque), surgical innovation (tylectomy), virotherapy (VCN-01), and immunotherapy (anti-GD2 approaches) are collectively expanding the therapeutic toolkit. The challenge ahead is to ensure that these advances translate into outcomes not just for well-resourced centres, but for every child with retinoblastoma, wherever they are born.

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How Far We Have Come with Intravitreal Chemotherapy

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Dr. Antonio Bechara Ghobril is an ophthalmologist whose international training reflects a strong commitment to excellence and innovation in eye care. After beginning his ophthalmology career in Switzerland and further refining his expertise in retinal diseases in Paris, he is currently pursuing advanced training in ocular oncology at Wills Eye Hospital in Philadelphia under the mentorship of Dr. Carol Shields. Dr. Bechara Ghobril combines academic rigor with a patient-centered approach to clinical care. His experience across diverse healthcare systems has shaped a broad and adaptable vision of modern ophthalmology. Beyond his clinical and academic pursuits, he has actively participated in humanitarian initiatives, using ophthalmology to expand access to care and contribute to underserved communities. His work reflects a dedication not only to advancing scientific knowledge, but also to creating meaningful impact through compassionate medicine.

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There was a time-not long ago-when a simple question would have been unthinkable: could we safely inject into an eye filled with tumor? In the setting of retinoblastoma, the answer for decades was an unequivocal "No!". The vitreous cavity was not merely avoided - it was feared. To cross it with a needle was to risk extraocular dissemination, a potentially fatal event. And so, when vitreous seeds persisted despite treatment, the decision was often final. The eye was removed.

But why were vitreous seeds so resistant? Why did even the most advanced therapies fail in this compartment? The answer lies in the biology of the vitreous itself. A relatively avascular and hypoxic environment, it limits drug penetration and creates what is, in effect, a pharmacologic sanctuary.[1] Tumor cells survive there, shielded from systemic circulation, protected from therapeutic concentrations, and capable of regrowth despite otherwise successful treatment. For years, this limitation defined the ceiling of eye salvage.

Then came a quiet but decisive turning point. In 1987, Kaneko et al. studied vitreous seeds and determined that melphalan was the most effective drug. He commenced intravitreal injection with melphalan 8 µg with variable control.[2] Shields watched Kaneko's trans pars plana injections and in 2006 treated 3 children with recurrent retinoblastoma in the vitreous cavity with seeding, using melphalan 8 µg, and all responded amazingly well but unfortunately recurred. In 2012, Munier et al.[3] asked a different question: what if the risk could be controlled? Their landmark study did not simply reintroduce intravitreal chemotherapy - it made it seem acceptable - sort of. Using a carefully designed safety technique - pars plana entry through a tumor-free quadrant, control of intraocular pressure to prevent reflux, and cryotherapy to sterilize the needle track - they administered intravitreal melphalan at doses of 20-30 µg every 7-10 days in 23 heavily pretreated eyes. The results were unprecedented, despite the use of concomitant treatments. Globe retention was achieved in 87% of cases, and all

Intravitreal chemotherapy matured. Each injection became an act of precision. The dose was tailored to tumor burden, ocular size, and prior treatment.

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She has authored or co-authored 12 textbooks, 341 chapters in edited textbooks, over 2000 articles in major peer-reviewed journals, and given over 1000 lectureships. The most prestigious awards that have honored her include the Donders Award (2003), the American Academy of Ophthalmology Life Achievement Honor Award (2011), Theodore Roosevelt Award and induction into the Academic All-American Hall of Fame (2011) for lifetime success in athletics and career. She was the President of the International Society of Ocular Oncology (2013-2015). Dr. Carol Shields is a member of numerous ocular oncology, pathology, and retina societies. She serves on the editorial or advisory board of 31 journals, including JAMA Ophthalmology and Retina.

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retained eyes achieved complete remission at a median follow-up of nearly two years. There were no cases of extraocular spread, despite the very risk that had once prohibited the technique. A localized salt-and-pepper retinopathy was observed in some eyes, reminding clinicians that toxicity persisted - but the balance had shifted. For the first time, Kaneko, Shields, and now Munier deemed that the vitreous cavity was no longer beyond reach.

So, it was shown that we could inject safely. But another question quickly followed: how much drug is enough - and how much is too much?

Almost simultaneously, across the Atlantic Ocean, Ghassemi, Shields, and Shields were working to define this balance.[4] At low doses of 8-10 µg, tumor control was inconsistent and often temporary. At the other extreme, 50 µg achieved strong control and cytotoxicity but at the cost of significant ocular damage: cataract, hemorrhage, severe hypotony, and even progression to phthisis bulbi, sometimes necessitating enucleation.[4]

Between these extremes lay a narrow therapeutic window. Experience from multiple centers converged toward 20-30 µg as the most effective and safest range. Administered on a repeated schedule every week to month, most eyes required a median of approximately four injections, to achieve complete regression of vitreous seeds.[3] With this approach, globe salvage rates rose dramatically to 87%, transforming outcomes for a disease that had once almost inevitably led to eye loss.[3,4]

And so, intravitreal chemotherapy matured. Each injection became an act of precision. The dose was tailored to tumor burden, ocular size, and prior treatment. Preparation of melphalan required strict timing due to its short half-life, and delivery demanded meticulous technique - small-gauge needle, careful entry through pars plana, cryotherapy withdrawal, and controlled distribution within the vitreous cavity. Success was no longer defined simply by tumor regression, but by the ability to achieve it without destroying the eye.

In a larger clinical series, Shields et al. confirmed these findings at scale. Using 20-30 µg of melphalan, often supplemented with 20 µg of topotecan when needed, they reported durable control of vitreous seeds, with a mean of approximately four injections per eye and globe salvage rates nearing 88%, without cases of metastasis or extraocular extension.[5]

Still, one concern remained: was it truly safe to inject these eyes? This question was addressed in a large international multicenter study by Francis, Abramson, Xi, et al involving more than 3500 intravitreal injections across over 700 eyes. There were no cases of extraocular tumor extension when appropriate safety precautions were used. Statistically, the risk was estimated to be less than 0.08% per injection. The fear that had once defined the field was no longer supported by evidence.[6]

And yet, another question persisted: could we achieve the same efficacy with less toxicity? Topotecan was subsequently introduced.[5] Initially explored cautiously, topotecan introduced a different pharmacologic paradigm. As a topoisomerase I inhibitor with a longer intraocular half-life and a more favorable retinal safety profile, it offered the possibility of sustained activity with reduced toxicity. At first, dosing remained conservative - around 20 µg in 0.1 mL - but even at these levels, topotecan demonstrated effective control of vitreous seeds with minimal retinal damage. Combination therapy quickly gained traction, allowing clinicians to reduce melphalan exposure while maintaining efficacy.[5]

Melphalan taught us the importance of limits. Topotecan revealed the possibility of flexibility. Together, they transformed intravitreal chemotherapy into a dynamic, individualized strategy.

The vitreous cavity is no longer a sanctuary for disease. It is a space we understand - measured in micrograms, guided by evidence, and shaped by the courage of those who first dared to ask: what if?

But could topotecan go further? Work by Abramson and Francis began to explore this question. In an early report, high-dose intravitreal topotecan at 90 µg was used to treat recurrent vitreous and subretinal seeds in 3 cases, and it worked but some of them received adjunctive therapy, with minimal retinal toxicity or functional impairment.[7] Then came the next evolution. In a subsequent series from Shields et al., intravitreal topotecan was administered at 90-100 µg across 81 injections in 25 eyes, demonstrating consistent tumor control with no local or systemic complications.[8] And finally, emerging global experience has further reinforced these findings. Vempuluru et al. evaluated high-dose intravitreal topotecan at 100 µg as monotherapy in a single-center series of refractory and recurrent intraocular retinoblastoma in 7 cases with 71% tumor control, and with particularly high efficacy for vitreous, epiretinal, and subretinal seeds, while responses in intraretinal tumors were more variable. Notably, complete globe salvage was achieved in all cases, with no significant functional retinal toxicity observed on electroretinography. These findings highlight both the potential and the limitations of high dose topotecan monotherapy and suggest that intravitreal chemotherapy can be adapted across diverse clinical settings.[9]

What does this progression tell us? It tells us that the field has evolved - not only technically, but philosophically. Melphalan taught us the importance of limits. Topotecan revealed the possibility of flexibility. Together, they transformed intravitreal chemotherapy into a dynamic, individualized strategy. Today, melphalan remains the backbone - used selectively at 20 µg for its potent cytotoxic effect - while topotecan provides adaptability, commonly used with doses ranging from 20 µg in combination therapy to 90-100 µg in monotherapy.

And so, the question that once defined the field has changed. We no longer ask, can we inject the eye? We no longer ask, does it work? We ask: what is the right drug, at the right dose, for this eye, at this moment?

This is how far we have come. From prohibition to precision. From fear to control. From enucleation to preservation. The vitreous cavity is no longer a sanctuary for disease. It is a space we understand - measured in micrograms, guided by evidence, and shaped by the courage of those who first dared to ask: what if?

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Aqueous Humor as a Clinical Safeguard: *Expanding Applications in Management of Retinoblastoma and RB-simulating Lesions*

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Introduction

Retinoblastoma (RB) affects nearly 8,000 children worldwide each year, posing a profound threat to life, ocular integrity, and vision.[1,2] Although RB has a known genetic etiology, progress toward precision medicine has been limited due to contraindication to direct tumor biopsy. While surgical removal of the eye enabled comprehensive molecular analysis, it provided only a single, end-stage snapshot of the disease. In contrast to other cancers, where serial biopsies can inform diagnosis, monitor treatment response, and reveal mechanisms of resistance, RB management has relied almost entirely on clinical examination by an experienced ocular oncologist. As a result, key questions about tumor evolution, therapeutic resistance, and clonal dynamics have remained largely inaccessible in real time.

This paradigm shifted in 2017, when our laboratory identified tumor-derived cell-free DNA (cfDNA) in the aqueous humor (AH) and pioneered its use as a liquid biopsy in RB.[3–5] Since then, we have demonstrated that AH can reliably detect high-risk genomic alterations, including chromosome 6p gain, BCOR mutations, and oncogene amplifications such as MYCN and MDM4—features associated with more aggressive disease biology.[6–8]

Building on these advances, LBSeq4Kids, a clinically validated targeted next-generation sequencing assay designed to detect somatic copy number alterations (SCNAs) and other clinically relevant genomic biomarkers from AH samples was developed at CHLA; the detection of either indicates the presence of ctDNA.[9] The test demonstrated a sensitivity of 98% for detecting ctDNA in active RB. LBSeq4Kids represents a major

LBSeq4Kids represents a major advance for intraocular malignancies, enabling molecular profiling to support accurate diagnosis, risk stratification, treatment response assessment, and disease surveillance.

advance for intraocular malignancies, enabling molecular profiling to support accurate diagnosis, risk stratification, treatment response assessment, and disease surveillance. We additionally have demonstrated that AH sampling is both safe—with a complication rate of just 0.08%—and superior to plasma as a liquid biopsy in retinoblastoma, as it provides eye-specific, more sensitive and comprehensive molecular profiling.[10,11]

In our experience, AH analysis has provided critical diagnostic and management insight in scenarios extending beyond genomic prognostication. Herein, we present a case series highlighting unique clinical situations in which AH analysis provided critical diagnostic or management insight, underscoring its expanding utility in RB.

Methods

We conducted a retrospective review of 13 patients in whom AH-derived molecular analysis was applied beyond conventional genomic risk stratification for RB. The surgical approach for AH sampling via paracentesis of the anterior chamber has been published previously.[12] All AH samples underwent cell-free DNA analysis using LBSeq4Kids as previously published.[9] Clinical data, imaging findings, molecular results, treatment course, and outcomes were reviewed.

This study was approved by the Institutional Review Board at Children's Hospital Los Angeles (CHLA). Written informed consent, including consent for publication and use of clinical images, was obtained from parents or legal guardians prior to study inclusion.

Case series

- **AH-guided exclusion of retinoblastoma**

In the following cases, we show that AH can be used to rule out malignancy in RB-simulating lesions.

Case 1: A 2-year-old male with a complex ocular history (Cataract Extraction with Intraocular Lens (CEIOL) OS, glaucoma s/p goniotomy, aphakia, corneal opacity) presented with a pigmented optic disc lesion OS with retinal incarceration and a stalk extending anteriorly with a white mass (Figure 1A-C). AH was taken to rule out possible malignancy in the setting of an ocular mass with foci of calcium, which did not reveal any pathogenic SCNAs in OS (Figure 1D).[13] This was consistent with lack of circulating tumor DNA (ctDNA) in the specimen, indicating no molecular evidence of malignancy. At 20-month follow-up, this patient was stable with no evidence of clinical progression to suggest malignancy.

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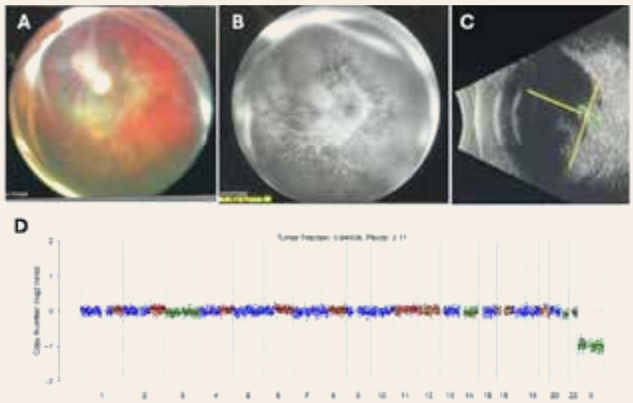

Figure 1: *(A-B) Fundus photographs demonstrating pigmented optic nerve lesion with anterior stalk and associated white mass. There was an area of calcification in the stalk and in the optic nerve mass with peripheral areas of bare choroid and RPE changes. (C) B-scan demonstrated an elevated intraocular lesion involving the optic nerve with foci of intralesional calcium with anterior stalk measuring 9.8 x 2.85 mm. (D) AH genomic profiling OS demonstrating absence of pathogenic SCNAs or detectable ctDNA.*

AH can be used to confirm malignant neoplastic processes including retinoblastoma, especially when the clinical presentation is atypical.

Case 2: An 8-year-old male with strabismus was found to have a translucent choroidal lesion OS with internal calcification. (Figure 2) There was no family RB history, and germline RB1 testing was negative. He was ultimately diagnosed with a retinoma and treated with laser. Given risk of transformation to RB and indeterminate malignant potential, AH was taken for analysis at diagnosis, which was negative for ctDNA and consistent with retinoma. This patient remains stable at 32-month follow-up.

Case 3: A 20-month-old female infant presented with several weeks of strabismus OD. Fundus examination revealed a fleshy mass with prominent intralesional vasculature and a stalk-like extension toward the lens through Cloquet's canal, associated with cataract, vitreous hemorrhage, and calcified vitreous seeds. (Figure 3) Given the atypical appearance, AH was obtained and demonstrated gains of 1q, 7q, 17q, and 18q with deletion of 17p, including the TP53 gene. Although not individually diagnostic,

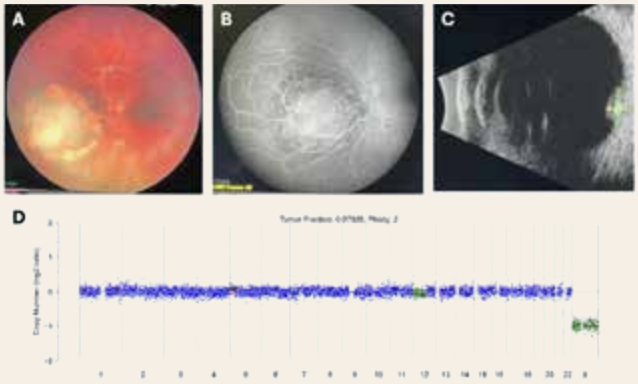

Figure 2: *(A) Fundus photograph of choroidal lesion with internal calcification consistent with retinoma with RPE changes. (B) Fluorescein angiography demonstrated no leakage. (C) B-scan ultrasonography of lesion measuring 7.5mm x 2.86 mm. (D) AH genomic profiling identifying absence of pathogenic SCNAs or detectable ctDNA.*

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AH-guided confirmation of malignancy

Conversely, AH can be used to confirm malignant neoplastic processes including retinoblastoma, especially when the clinical presentation is atypical.

these alterations were highly consistent with an active malignancy and supported a diagnosis of diffuse infiltrating RB. Germline RB1 testing was negative. The patient subsequently underwent primary enucleation, and histopathology confirmed diffuse infiltrating RB. At four-month follow-up, she remains clinically stable

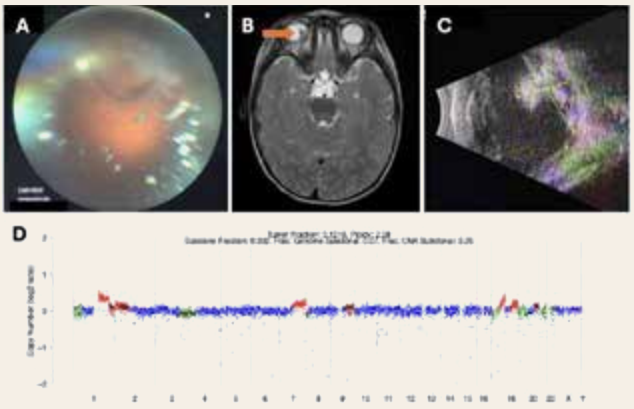

Figure 3: *(A) Fundus photography demonstrating stalk-like intraocular tumor with vitreous seeding. (B) MRI demonstrating diffusely nodular hypercellular tumor along posterior aspect of the right globe with components appearing to extend toward the lens, possibly along Cloquet's canal. (C) B-scan US of the lesion measuring 7.96 mm x 14.03 mm. (D) Corresponding AH genomic profile OD showing pathogenic SCNAs consistent with malignancy.*

without evidence of recurrence.

Case 4: A 7-year-old male with a previously stable untreated retinoma was referred for interval change. Examination demonstrated a fibrotic dome-shaped with fine vascularity and central calcification (Figure 4A-B). Due to evolving calcification and increasing vasculature within the tumor, AH was obtained and demonstrated a complex pattern of alterations involving almost all chromosomes (Figure 4C), which was consistent with a malignant neoplastic process. Findings were most consistent with retinoma with malignant transformation, and thus, laser consolidation was performed. Repeat AH analysis after treatment was negative for ctDNA. At 57 month follow-up, he remains clinically stable without evidence of recurrence.

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Case 5: A 3-month-old female presented with a several-week history of leukocoria. She was diagnosed with unilateral Group D/cT2b RB OS with extensive vitreous seeding obscuring the optic nerve. Diagnostic MRI showed no optic nerve or CNS involvement; RB1 germline testing was negative. Following 4 cycles of intra-arterial melphalan and topotecan, the tumor regressed clinically, but dense calcified vitreous seeds precluded visualization of the retina and nerve. AH liquid biopsy remained positive for ctDNA, prompting 5 serial intravitreal melphalan (IVM) injections until ctDNA

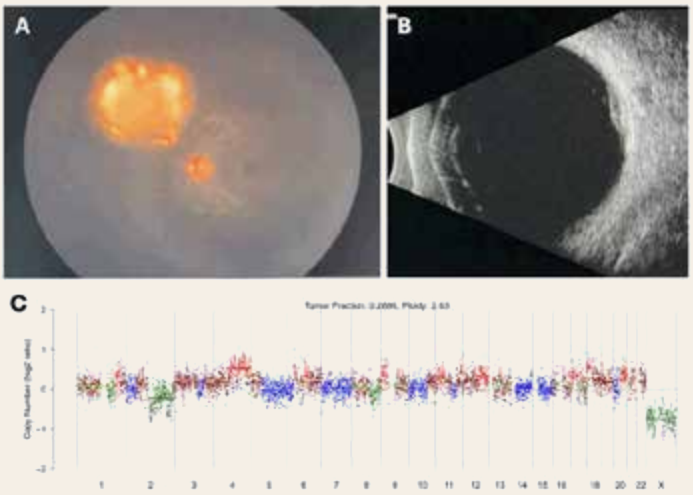

Figure 4: *(A) Fundus photograph of partially calcified retinoma with increased vascularity. (B) B-scan ultrasonography of lesion measuring 2.96 mm x 7 mm. (C) AH genomic profiling demonstrating complex chromosomal alterations consistent with malignant transformation. This included a partial gain of chromosome 6, and a gain and loss involving the long arm of chromosome 1.*

AH-guided management of RB

Loss of view from cataract, vitreous seeding or hemorrhage presents a significant diagnostic challenge in RB, limiting assessment of intraocular tumor activity and procedural safety. We have previously demonstrated the utility of AH in detecting recurrent disease in the setting of vitreous hemorrhage[14]. In such cases with obscured visualization or clinically equivocal findings, AH offers additional molecular information to guide management in RB and support safer intraocular intervention.

clearance was achieved (Figure 5). Repeat MRI remained negative for any optic nerve or CNS involvement. AH remained negative 5 months after final treatment, and at 12-month follow-up, she achieved complete response in all ocular compartments by RECIST-RB guidelines.[15] There is still no view to any posterior pole structures.

In cases with obscured visualization or clinically equivocal findings, AH offers additional molecular information to guide management in RB and support safer intraocular intervention.

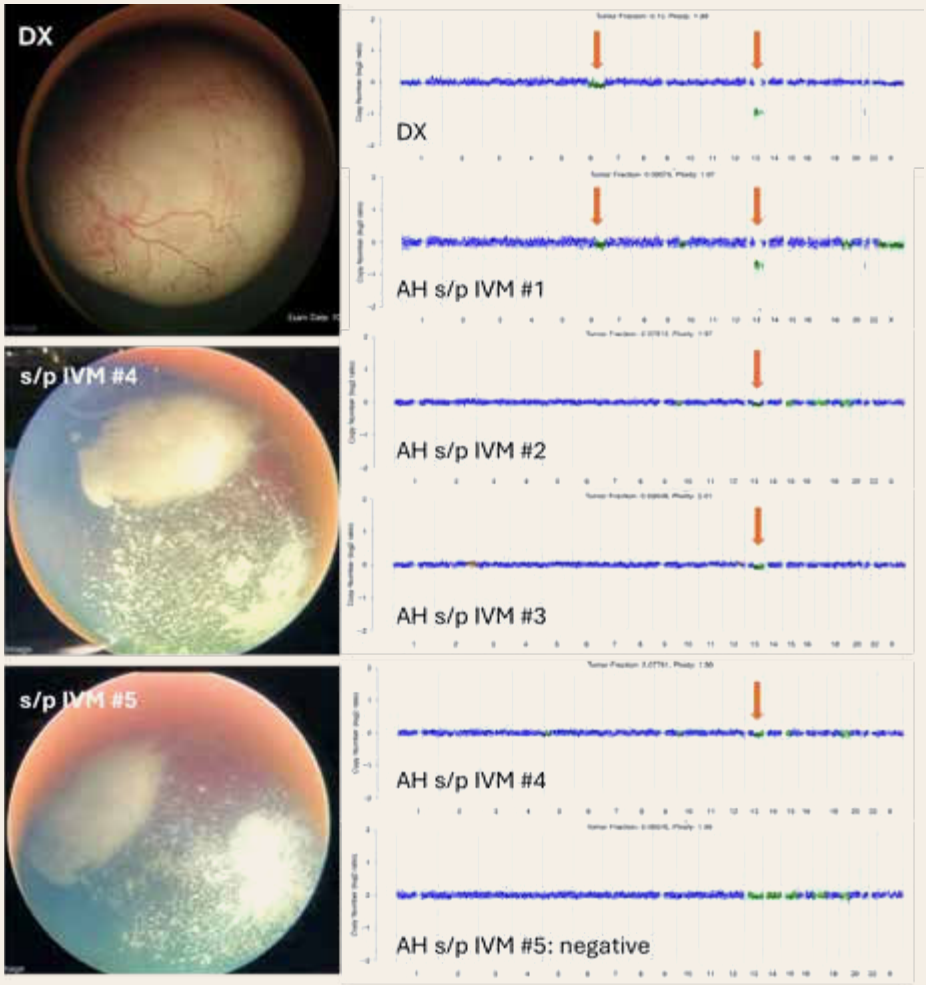

Figure 5: *Longitudinal AH genomic profiling demonstrating persistent ctDNA positivity despite limited clinical visualization, followed by clearance after the fifth-cycle of intravitreal chemotherapy. At IVM #5, minor genomic fluctuations were observed diffusely; however, these lacked the focal alterations seen previously and were therefore interpreted as negative for active tumor-associated ctDNA.*

Case 6: A 2-year-old male with bilateral RB (Group D/cT2b OD, Group E/cT3e OS) underwent multimodal therapy including systemic chemotherapy, IAC, and intravitreal chemotherapy. Serial AH analysis initially demonstrated pathogenic SCNAs in both eyes, which subsequently cleared following treatment. Prior to cataract extraction OS, AH confirmed absence of detectable ctDNA, supporting lack of active intraocular disease and procedural safety. At 29-month follow-up, he remained stable post-posterior chamber intraocular lens (PCIOL) implantation, without disease recurrence.

AH liquid biopsy identified molecular evidence of recurrent or evolving RB prior to definitive clinical progression, informed risk-adapted surveillance, and detected actionable genomic alterations relevant to treatment selection. Serial AH profiling also distinguished recurrent disease from molecularly distinct secondary tumors.

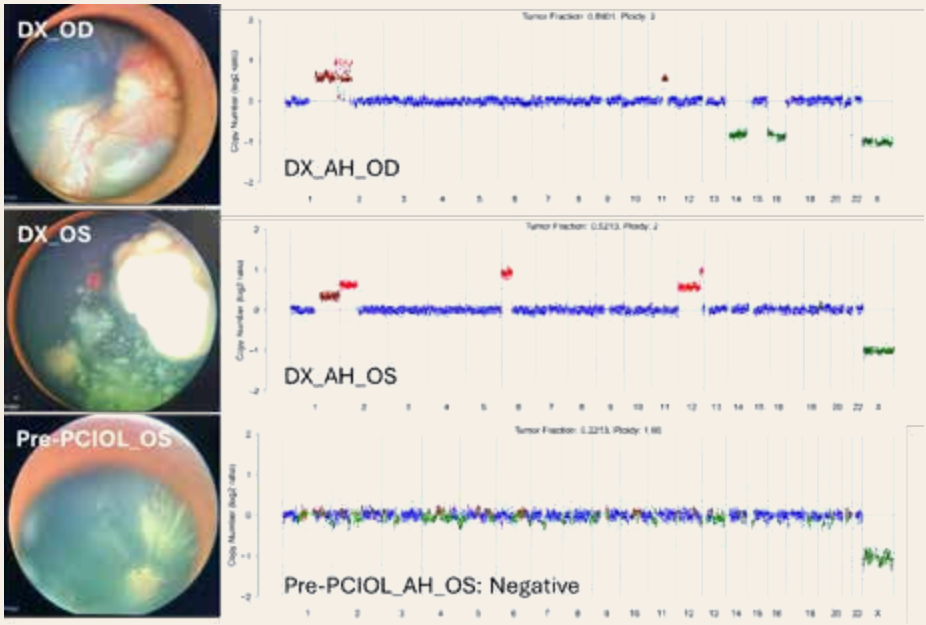

Figure 6: *Fundus photos and corresponding genomic profiles: AH analysis of OD revealed gain of the long arm of chromosome 1, three or more copies of alternating regions within the short arm of chromosome 2, gain within 11q, loss of 14 and 16, and loss of the very distal long arm of 21. AH analysis of OS demonstrated 1q, 2p, 6p, and chromosome 12. Serial AH analysis demonstrated clearance of tumor-derived ctDNA prior to intraocular surgery in treated bilateral RB.*

Utility of AH in detection of recurrence

Next, we describe cases in which AH liquid biopsy identified molecular evidence of recurrent or evolving RB prior to definitive clinical progression, informed risk-adapted surveillance, and detected actionable genomic alterations relevant to treatment selection. Serial AH profiling also distinguished recurrent disease from molecularly distinct secondary tumors.

Case 7: A 2-year-old female with bilateral RB (Group B/cT1b OD; Group D/cT2b OS) and germline RB1 mutation (deletion exons 1-17) developed recurrent disease OD two years after initial treatment. AH liquid biopsy at recurrence demonstrated a new MDM4 amplification. (Figure 7) Given evidence suggesting increased responsiveness to topotecan in MDM4-amplified tumors[8], treatment was tailored with intravitreal topotecan (IVT) therapy. Persistent ctDNA positivity has paralleled disease activity during follow-up after 4 IVT injections, and treatment is ongoing. This case demonstrates the potential of AH profiling to identify actionable genomic alterations that may guide treatment selection.

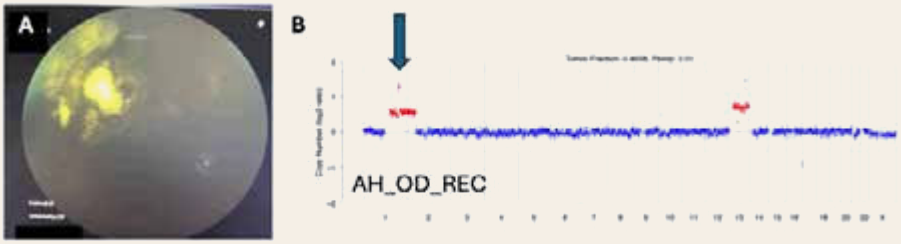

Figure 7: *(A) Fundus photo OD demonstrating active retinal recurrence extending to the ora and (B) genomic profile demonstrating MDM4 at recurrence (blue arrow).*

Case 8: A 7-month-old male was diagnosed with bilateral RB (Group C/cT1b OD; Group E/cT3c OS). There was no family history of RB; genetic testing identified a heterozygous pathogenic RB1 variant (NM_000321.3: c.1723C>T). Diagnostic AH analysis showed MYCN amplification OD and gains of 1q and 6p OS. Despite clinical stability after completion of systemic chemotherapy, AH surveillance continued to demonstrate persistent MYCN amplification in OD. Given ongoing ctDNA positivity, the patient underwent close monitoring and developed a small scar recurrence four weeks later concordant with the prior AH findings, which was treated with laser. (Figure 8) Persistent ctDNA positivity may therefore precede clinically detectable recurrence and identify eyes requiring closer surveillance.

Case 9: A 9-month-old female with Group D/cT2b RB OD demonstrated diagnostic AH positivity with 6p gain. RB1 germline testing was positive (NM_000321.3: c.1960+5G>A), although clinically she remained with unilateral disease only. Following three cycles of IAC with melphalan and topotecan, a new peripheral tumor developed 20-months later. Repeat AH analysis demonstrated a distinct genomic profile, including 1q gain, 5p gain, and 16q loss, supporting development of a molecularly distinct second tumor rather than recurrence from residual seeds. The lesion responded to focal cryotherapy and laser therapy, and she remains stable as of 21-month follow-up. (Figure 9)

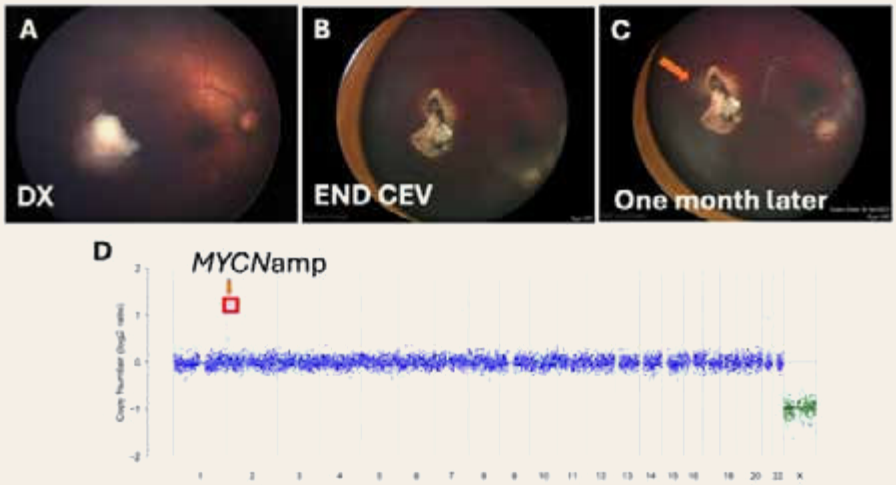

Figure 8: *Serial fundus photos demonstrating (A) lesion at diagnosis, (B) clinical regression of lesion after completion of systemic chemotherapy (END CEV), (C) scar recurrence four weeks after END CEV. (D) Genomic profile demonstrating MYCN amplification at END CEV.*

Although AH liquid biopsy has demonstrated high sensitivity in RB, its performance may be more limited in slowly growing choroidal malignancies with lower ctDNA shedding.

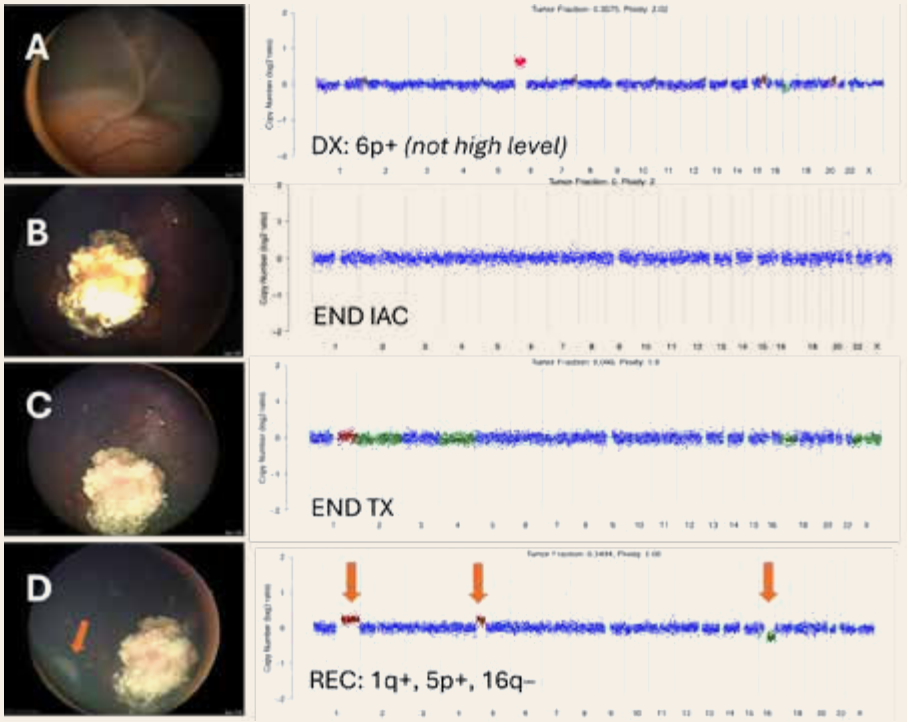

Figure 9: *Fundus photo and correlating genomic profiles at (A) diagnosis, demonstrating a predominantly exophytic tumor with significant dilated vasculature, retinal detachment, vitreous dust and subretinal seeding; (B) end of intra-arterial chemotherapy; (C) 6-months after last treatment; and (D) new tumor at the ora forming 20-months after diagnosis, which was subsequently treated with cryotherapy.*

- **AH evaluation of choroidal neoplasms**

Although AH liquid biopsy has demonstrated high sensitivity in RB, its performance may be more limited in slowly growing choroidal malignancies with lower ctDNA shedding. Herein, we describe a pediatric choroidal melanoma in which AH analysis was negative despite clinically confirmed malignancy.

Case 10: A 9-year-old girl presented with a pigmented choroidal mass associated with subretinal fluid and orange pigment (Figure 10A-C). Given the rarity of pediatric choroidal melanoma, AH liquid biopsy was performed but did not reveal any pathogenic SCNAs (Figure 10D). Germline testing identified a BAP1 alteration, and the lesion was diagnosed clinically as choroidal melanoma. Following plaque brachytherapy, the patient remained stable as of 11-month follow-up. This case highlights the lower sensitivity of AH ctDNA detection in slowly growing choroidal tumors, which likely shed less ctDNA than retinal tumors such as RB during tumor necrosis.

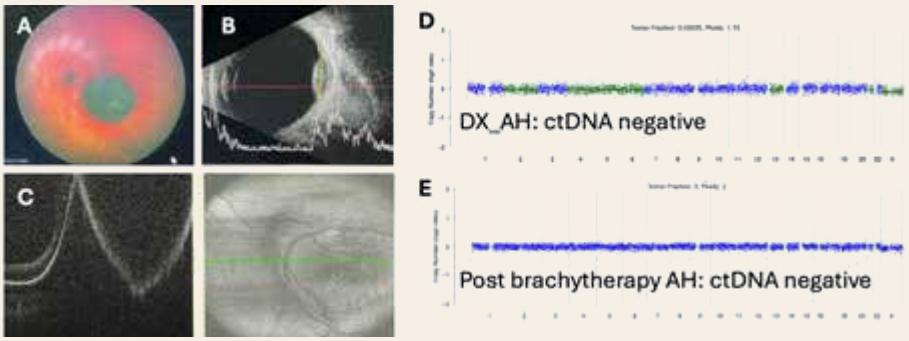

Figure 10: *(A) Fundus imaging demonstrated pigmented choroidal lesions with subretinal fluid and orange pigment. (B) B-scan US demonstrated an elevated choroidal dome-shaped intraocular lesion measuring 8.95mm x 3.10mm with retinal detachment. (C) OCT through the lesion demonstrates subretinal fluid. (D) AH genomic profile with absence of detectable pathogenic SCNAs.*

- **AH-identified unique germline alterations**

While germline RB1 alterations are the most commonly identified inherited variants in RB, AH liquid biopsy may also reveal additional clinically significant germline alterations, such as BRCA1 and FANCL. Herein, we describe cases in which AH and plasma profiling identified unexpected cancer-associated variants, highlighting the broader utility of AH analysis for genetic risk stratification beyond tumor diagnosis alone.

Case 11: A 2-year-old female presented with leukocoria and was diagnosed with unilateral Group E/cT3c RB OS. MRI demonstrated a large subretinal mass with abnormal enhancement and focal interruption of the normal chorioretinal interface, concerning for 4 mm of post-laminar optic nerve involvement. Due to extraocular extension, she was treated with systemic chemotherapy per ARET0321 (cyclophosphamide, cisplatin, etoposide, and vincristine). AH and plasma LBSeq4Kids analysis demonstrated high-level 6p gain, while targeted sequencing identified pathogenic germline alterations in RB1 (NM_000321.3:c.607+1G>T, VAF 44.4%) and FANCL (NM_018062.4:c.335C>G, VAF 46.7%). (Figure 11) Germline RB1 testing subsequently confirmed the same alteration identified in AH. Following two cycles of chemotherapy, there was marked regression of both intraocular and optic nerve disease prior to enucleation OS. This case highlights the ability of AH to identify clinically relevant germline alterations beyond RB1, including FANCL, a DNA repair gene associated with Fanconi anemia pathway dysfunction and cancer susceptibility.

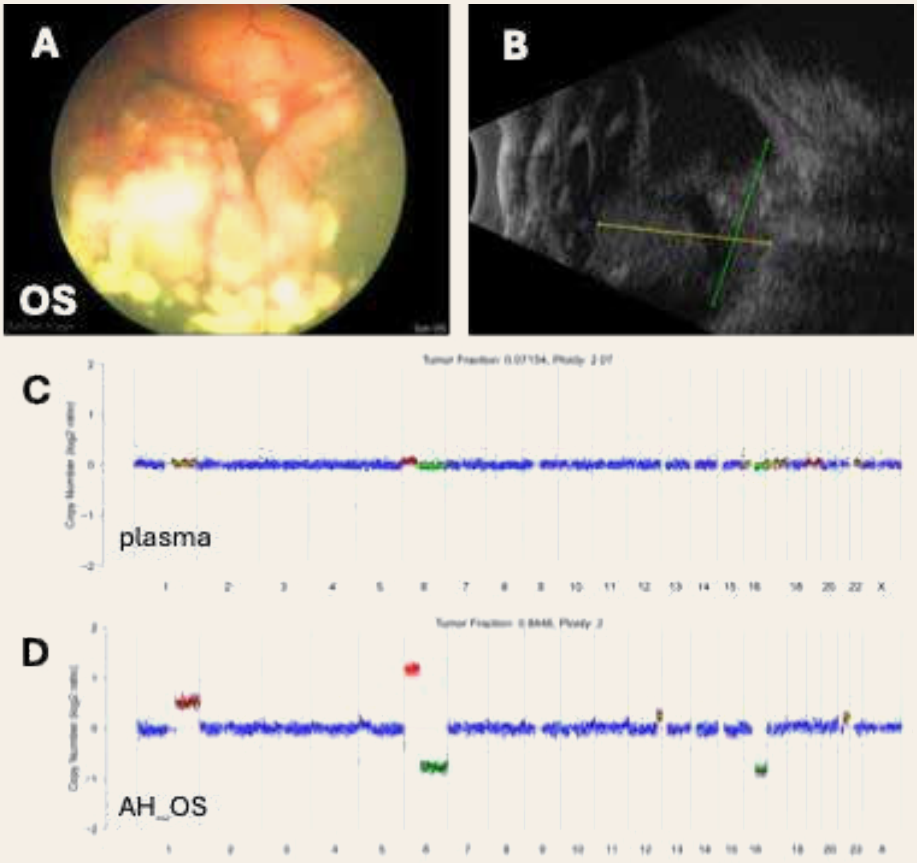

Figure 11: *(A) Diagnostic fundus exam revealed large predominantly exophytic tumor which directly involves the macula, with complete retinal detachment and extensive subretinal and vitreous seeding OS. (B) B-scan US demonstrated a dome-shaped intraocular lesion with scattered diffuse intralesional calcium measuring 13 x 13 mm. Genomic profiling from (C) plasma demonstrating 6p gain and (D) AH demonstrating gains in 1q, 6p, and 12p, and losses in 6q and 16q.*

AH liquid biopsy may also reveal additional clinically significant germline alterations, such as BRCA1 and FANCL.

Case 12: An 18-month-old male with a family history of Leber's congenital amaurosis (LCA) in the father and delayed motor milestones was diagnosed with unilateral Group D/cT3c RB OD. (Figure 12) AH analysis identified gains involving 5q, 6p, 7q, and 9q, along with a focal interstitial deletion at 13q14 encompassing the RB1 gene. Plasma LBSeq4Kids analysis demonstrated the same 13q14 deletion, raising concern for a germline 13q deletion syndrome. The patient was also found to be a heterozygous carrier of an NMAT1 variant, known to cause LCA, consistent with family history. The patient was treated with IAC with a favorable treatment response. This case highlights the utility of AH liquid biopsy in identifying tumor-specific genomic alterations and uncovering a likely germline 13q deletion, demonstrating its role in both oncologic management and broader genetic risk stratification.

Case 13: A 20-month-old male with bilateral RB (Group D/cT2b OD, Group E/cT3b OS; Figure 13A-B) underwent multimodal therapy, including 6 cycles of systemic chemotherapy and 7 intravitreal injections OU. Despite treatment, OS retained a persistent nodular lesion concerning for active tumor (Figure 13C). Because the eye had poor visual potential and further IAC was poorly tolerated, the family elected to proceed with secondary enucleation. AH liquid biopsy was performed on AH taken immediately after enucleation and demonstrated no detectable ctDNA (Figure 13C), compared with somatic CNAs found on initial diagnostic AH analysis (Figure 13A-B). Histopathology also revealed no viable tumor, concordant with the AH findings. This case demonstrates the potential role of AH analysis in distinguishing inactive scar tissue from viable tumor when clinical findings are equivocal.

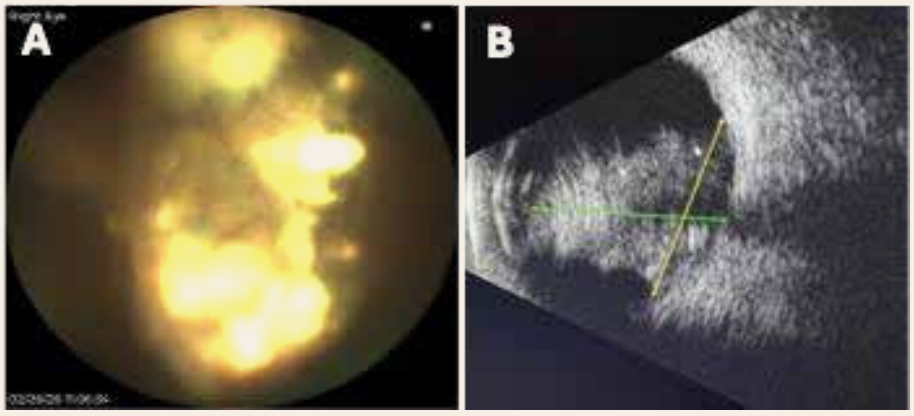

Figure 12: *(A) Diagnostic fundus images demonstrating a large predominantly endophytic tumor overlying the optic nerve. (B) B-scan US demonstrated a 14 × 14 mm intraocular mass with scattered intralesional calcifications.*

AH-guided identification of inactive disease

Herein, we describe a case in which AH liquid biopsy accurately identified absence of active tumor despite persistent clinically suspicious findings after treatment.

AH liquid biopsy has transformed RB management by enabling tumor-derived genomic profiling in the absence of direct tissue biopsy.

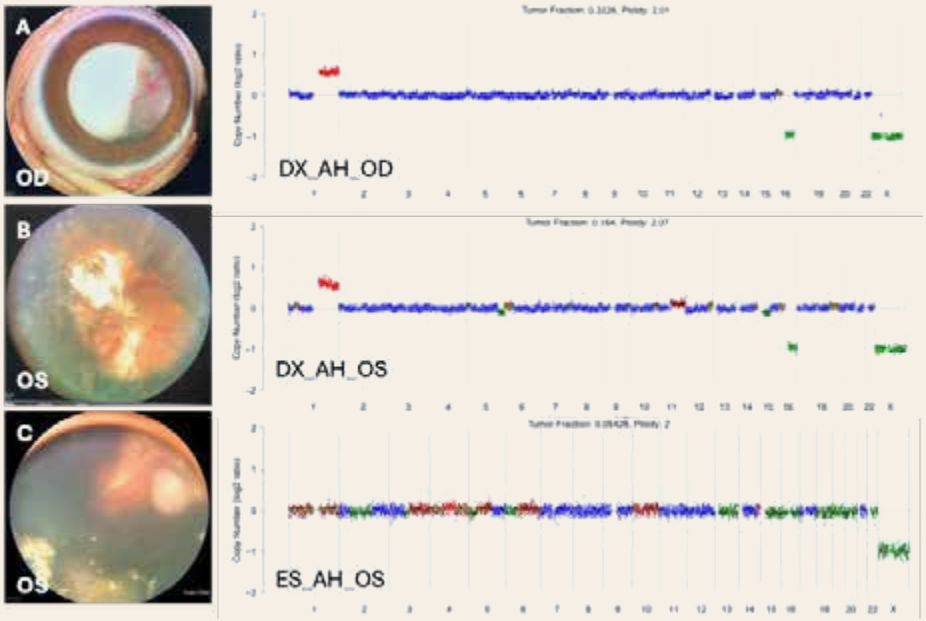

Figure 13: *Fundus exam and correlating genomic profiles at (A-B) diagnosis OU, demonstrating gain in 1q, and at (C) enucleation OS, demonstrating no pathogenic SCNAs in AH.*

Discussion

AH liquid biopsy has transformed RB management by enabling tumor-derived genomic profiling in the absence of direct tissue biopsy. While its role in molecular risk stratification has been well established, we have identified unique cases in which AH liquid biopsy serves as a versatile tool that supports clinical decision making across a spectrum of diagnostic and therapeutic scenarios.

In cases with atypical clinical or radiographic features, AH analysis provided objective molecular context. The absence of tumor-associated genomic alterations supported conservative management in lesions clinically concerning for RB, while detection of RB-consistent copy number changes strengthened diagnostic confidence in atypical presentations. Importantly, AH results were interpreted in conjunction with clinical findings; molecular data alone are not independently diagnostic. Nevertheless, they provide a powerful adjunct when ophthalmoscopic or imaging features are ambiguous.

A second critical application was longitudinal molecular monitoring. In several cases, AH demonstrated clearance of tumor-derived DNA despite persistent or clinically indeterminate vitreous debris. Conversely, persistent ctDNA following apparent regression preceded clinical recurrence. In RB, where visualization may be limited by media opacity, calcification, retinal detachment, or persistent seeding, AH-derived ctDNA offers a uniquely accessible window into intraocular tumor biology.

AH also informs therapeutic strategy. Identification of emerging genomic alterations at recurrence, including MDM4 amplification, influenced intravitreal chemotherapy selection. In other cases, molecular profiling distinguished new tumors from recurrences based on distinct alteration patterns. These observations suggest that AH profiling may enable dynamic genomic characterization over time, supporting a precision-medicine approach rather than static risk assignment at diagnosis.

An additional clinically meaningful application was procedural risk mitigation. Historically, intraocular

Rather than functioning solely as a surrogate tumor biopsy for baseline genomic characterization, AH emerges as a dynamic biomarker of disease presence, activity, and evolution.

surgery in RB has been approached with caution due to concerns for tumor dissemination. In selected cases requiring cataract extraction or other intraocular intervention, confirmation of absent detectable tumor-derived DNA provided additional reassurance prior to surgical manipulation. While a negative AH result cannot definitively exclude microscopic disease, it offers complementary risk stratification in carefully selected clinical contexts.

Collectively, these cases support a conceptual shift in how AH liquid biopsy is viewed. Rather than functioning solely as a surrogate tumor biopsy for baseline genomic characterization, AH emerges as a dynamic biomarker of disease presence, activity, and evolution. Its integration into clinical decision-making may enhance diagnostic precision, refine therapeutic selection, improve monitoring when examination is limited, and potentially anticipate recurrence.

Limitations of this study include retrospective experience from a single tertiary center, and case heterogeneity limiting generalizability. AH was also notably less sensitive in identifying choroidal malignancy. Despite these limitations, our findings demonstrate that AH liquid biopsy can meaningfully influence clinical care across multiple domains in pediatric ocular oncology as demonstrated by this collection of unique cases. As sequencing technologies advance and our understanding of RB tumor evolution deepens, AH-based molecular profiling may play an increasingly central role in personalized RB management.

Conclusion

In these contexts, AH analysis functioned not only as a molecular diagnostic tool but also as a clinical safeguard. Applications included confirming absence of tumor-derived DNA prior to intraocular intervention, assessing for active seeding when visualization was limited, guiding surgical timing in eyes with poor posterior segment view, and monitoring for molecular evidence of residual or recurrent disease. Collectively, these cases redefine the role of AH liquid biopsy from a prognostic adjunct to an active clinical decision-support tool that enhances diagnostic certainty, procedural safety, and personalized management in RB care.

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The Question After the Diagnosis: *What TCGA Really Changed in Uveal Melanoma*

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There is a moment in clinic that every ocular oncologist knows. You sit with a patient, often someone who walked in not knowing what to expect. You have the ultrasound. You have the photographs. And then you say the words: *"You have a uveal melanoma."*

The consultation changes shape immediately. First comes the diagnosis: *I have cancer in my eye?* Then treatment. *Will I lose the eye? Are there other options?* And then comes the quieter, often harder question: *"What happens to me now?"* Prognostication in uveal melanoma was once imprecise. We could talk about tumor size, ciliary body involvement, extrascleral extension. But for the person in front of us, these answers often felt inadequate. We could explain what we planned to do to the eye, yet struggle to say what the future might look like. How great was the risk of metastasis? How frequently should they have liver imaging? How should they live with the uncertainty? That is why prognostication matters so deeply in uveal melanoma. It shapes counseling, follow-up, family planning, work decisions, and the psychological burden patients carry long after the plaque is removed.

And that is where TCGA changed the conversation. The Cancer Genome Atlas, or TCGA, gave us a more refined cytogenetic framework for understanding uveal melanoma. This classification offered a biologically grounded staging based on chromosomal alterations,

Prognostication matters so deeply in uveal melanoma. It shapes counseling, follow-up, family planning, work decisions, and the psychological burden patients carry long after the plaque is removed. And that is where TCGA changed the conversation.

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especially involving chromosomes 3 and 8. From this came the familiar TCGA groups A through D, ranging from lower to higher metastatic risk. For clinicians, the value of TCGA is this: it turned a vague sense of risk into something more structured, that guides how we counsel and monitor patients.

One of the most striking demonstrations of that came from work showing just how sharply prognosis separates across TCGA classes. Compared with class A, the 5-year hazard ratio for metastasis rose to 4.1 in class B, 10.1 in class C, and 30.0 in class D. For death, the increase was similarly sobering: 3.1 for class C and 13.7 for class D, with no deaths in class B.[1] In plain language, TCGA classes are not just labels. They behave like different diseases. That matters in clinic. A patient with a class A melanoma is not hearing the same story as a patient with class D disease. Both have uveal melanoma, but one may face a relatively favorable course while the other carries a very high metastatic risk. Before cytogenetic stratification, these patients might have been counseled in much the same way. Now, increasingly, they should not be.

Another study pushed this further by showing that TCGA class is not floating in isolation from the rest of what we see clinically.[2] It is tied to phenotype. When patients were compared across groups A to D, there were meaningful differences in age at diagnosis, with median ages rising from 57 in group A and 53 in group B to 61 in group C and 63 in group D. Visual acuity at presentation also worsened across the groups: good presenting vision in the 20/20 to 20/50 range was seen in 80% of group A, falling to 67% in group B, 70% in group C, and 65% in group D. The tumors themselves looked progressively more threatening too. Median thickness increased from 3.5 mm in group A to 5.2 mm in group B, 6.0 mm in group C, and 7.1 mm in group D. Diameter rose from 10 mm to 13 mm to 14 mm to 16 mm. In other words, the higher-risk cytogenetic groups tended to be older patients with larger tumors and somewhat poorer visual function at presentation.

This study also showed what every clinician wants to know most: how those groups translate into metastatic outcomes over time. At 5 years, survival was 96% in group A, 86% in group B, 62% in group C, and 37% in group D. At 10 years, it was 93% for group A, 78% for group B, and 50% for group C, with data for group D not available in that analysis. Multivariate analysis showed stepwise worsening in risk moving from B vs. A, C vs. B, and D vs. C, even while tumor thickness and diameter remained independently important. That last point is worth pausing on. TCGA did not make traditional clinical features irrelevant. It made them more intelligible. Tumor size still matters. Thickness still matters. Diameter still matters. But now we can see them alongside tumor biology rather than instead of it.

Of course, once one begins thinking biologically, other old assumptions need revisiting. Take tumor location. We often have instincts about where tumors "feel" more dangerous. Central tumors may be caught earlier because they affect vision. Peripheral tumors may grow quietly for longer. One study found that uveal melanoma in the central region was indeed smaller in thickness and base, and appeared to demonstrate more favorable metastasis-free survival compared with other quadrants, clock hours, and anteroposterior zones.[3] At first glance, that might tempt us to think location itself carries prognostic power. But the more interesting finding came after adjustment: when tumor size and proximity to the foveola and optic disc were taken into account, location alone offered no independent benefit across the 49 analyzed zones. In other words, central tumors may seem to do better

TCGA did not make traditional clinical features irrelevant. It made them more intelligible. Tumor size still matters. Thickness still matters. Diameter still matters. But now we can see them alongside tumor biology rather than instead of it.

Most importantly, TCGA offers patients something that medicine too often withholds when certainty is impossible: a framework. It helps narrow uncertainty, even if it cannot remove it.

largely because they are caught earlier, not because the location itself is kinder.

And this brings us back to an old truth in ocular oncology: size still matters, even in the molecular era. In a long-term study, mean thickness was 2.5 mm for small tumors, 5.0 mm for medium tumors, and 10.2 mm for large tumors.[4] Over 25 years, non-conditional metastasis rates were 5%, 12% and 21%, respectively. Even after years without metastasis, size continued to matter. Among patients that remained metastasis-free at 3 years, the 25-year incidence of metastasis was 7% for small, 13% for medium, and 26% for large tumors. At 5 years metastasis-free, the 25-year rate of metastasis was 6%, 11%, and 21%; and at 10 years metastasis-free, the 25-year rate was 4%, 8%, and 21%. In order words, risk declines with time, but it does not disappear. In fact, hazard ratios comparing medium with small tumors, and large with medium tumors, remained elevated even after 3, 5, or 10 years without metastasis.

So where does this leave us in daily practice? In a better position. Not perfect, but better. When we diagnose uveal melanoma now, we are still talking about local treatment, globe preservation, radiation complications, and visual outcomes. But we are also increasingly able to speak a more precise language about metastatic risk. We can explain that prognosis is shaped by both clinical features and tumor cytogenetics. We can separate low-risk from high-risk disease more credibly than before. We can justify why one patient might reasonably undergo less intensive surveillance while another may merit much closer systemic monitoring.

Most importantly, TCGA offers patients something that medicine too often withholds when certainty is impossible: a framework. It helps narrow uncertainty, even if it cannot remove it. It has made prognostication in uveal melanoma more nuanced, more biologically faithful, and more clinically useful.

There is still plenty we do not know. We still cannot predict every metastasis. We still need better systemic therapies and better ways of integrating genomic information into everyday care. But we are no longer where we were. We are no longer limited to saying, *"We know how to treat the tumor, but beyond that we cannot tell you much."* Now we can say more: not all uveal melanomas are the same; chromosomes matter; tumor size and tumor biology work together in prognosis; and surveillance should not be one-size-fits-all.

Maybe that is the real contribution of TCGA. Not simply that it stratified risk, but that it made our conversations truer. Because after "*You have a uveal melanoma,*" the next question is still, *"What happens to me now?"* At least now, we can answer it better.

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Uveal Melanoma in 2026: *From Molecular Stratification to Early Systemic Intervention*

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With over seven years of experience in vitreoretinal surgery and ocular oncology in India, she has contributed extensively to clinical care, research, and academics, including establishing ocular oncology services in Eastern India.
She has actively presented her work at national and international meetings and has been involved in multiple clinical research projects and publications in ophthalmology. Outside work, she enjoys reading, traveling, singing, and fitness.

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Introduction

Uveal melanoma represents one of the most intriguing paradoxes in ocular oncology: while local tumor control is achieved with high success, a substantial proportion of patients ultimately develop metastatic disease, often years after initial treatment. This delayed yet persistent risk, predominantly involving the liver, highlights the fundamentally systemic nature of the disease from an early stage. Despite advances in plaque brachytherapy, proton beam therapy, and surgical management, survival outcomes in metastatic uveal melanoma have historically remained poor.[1]

Over the past decade, however, the field has undergone a significant transformation. Advances in molecular profiling, gene expression analysis, systemic therapy, and translational research have shifted clinical practice toward a biology-driven approach.[1] This paradigm emphasizes individualized risk stratification and early systemic intervention, with the goal of not only treating metastatic disease but also better understanding its natural history.

Genetic risk stratification

The molecular landscape of uveal melanoma is now well characterized, with early driver mutations such as GNAQ and GNA11 present in majority of the tumors. However, these mutations alone do not determine clinical behavior. Instead, prognosis is largely dictated by secondary genetic events, which define metastatic potential and guide clinical decision-making.[1,2]

- **Gene expression profiling and PRAME**

Gene expression profiling (GEP) has become central to prognostication in uveal melanoma, classifying tumors into Class 1 (low metastatic risk) and Class 2 (high metastatic risk). This system has significantly improved risk prediction beyond traditional clinical parameters such as tumor size and location.[2]

The addition of PRAME (Preferentially Expressed Antigen in Melanoma) has further refined this classification. PRAME expression within Class 1 tumors identifies a subgroup with significantly higher metastatic risk, effectively bridging the gap

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between low- and high-risk categories.[2] This has direct clinical implications, allowing clinicians to tailor surveillance strategies and identify patients who may benefit from closer monitoring or inclusion in adjuvant therapy trials.

- **TCGA classification, BAP1, and tumor thickness**

The Cancer Genome Atlas (TCGA) classification provides another complementary genomic framework, stratifying uveal melanoma into four molecular groups (A–D) based on chromosomal alterations and mutations such as BAP1, SF3B1, and EIF1AX.[3]

Among these, BAP1 (BRCA1-associated protein 1) has emerged as the most critical prognostic marker. Loss of BAP1 expression is strongly associated with monosomy 3 and is linked to aggressive tumor biology, early metastatic spread, and poor survival outcomes.[4] Patients with BAP1-mutated tumors are now routinely classified as high-risk and often undergo more intensive systemic surveillance.

Importantly, large cohort studies have demonstrated that tumor thickness significantly modifies metastatic risk within each genetic subgroup.[3,4] Patients with thicker tumors show progressively worse metastasis-free survival across all TCGA classes. Work from Shields and colleagues has emphasized that combining tumor size with molecular classification provides a more clinically meaningful prognostic model, enabling risk-adapted surveillance and patient counseling.[4]

- **Emerging genetic subsets: MBD4**

A recently recognized subset involves MBD4 (methyl-CpG binding domain protein 4) mutations. These tumors exhibit a hypermutated phenotype due to defective DNA repair mechanisms, in contrast to the typically low tumor mutational burden of uveal melanoma.[5]

This distinction is clinically significant, as MBD4-mutant tumors may demonstrate increased responsiveness to immunotherapy. Although relatively rare, this subgroup highlights the biological heterogeneity of uveal melanoma and supports the transition toward precision oncology.[5]

Systemic therapy and neoadjuvant strategies

- **Tebentafusp: Changing the treatment landscape**

The development of tebentafusp, a bispecific T-cell receptor therapy targeting gp100, represents a major breakthrough in the management of uveal melanoma. In a landmark phase III trial, tebentafusp demonstrated a significant overall survival benefit compared with standard therapy, marking the first systemic treatment to improve outcomes in metastatic disease.[6]

However, tebentafusp is restricted to patients with HLA-A*02:01, limiting its applicability to approximately half of the population. Despite this limitation, its success has prompted a shift toward earlier systemic intervention. Ongoing clinical trials are evaluating tebentafusp in neoadjuvant and adjuvant settings, particularly in high-risk patients, with the aim of targeting micrometastatic disease before clinical progression.[6]

- **Darovasertib and combination strategies**

Targeted therapy has emerged as a promising complementary approach. Darovasertib (IDE196), a protein kinase C (PKC) inhibitor, targets a key downstream pathway of GNAQ and GNA11 mutations. Early-phase clinical trials combining darovasertib with crizotinib have demonstrated encouraging results, including objective response rates exceeding 30% and improved

A recently recognized subset involves MBD4 mutations. These tumors exhibit a hypermutated phenotype due to defective DNA repair mechanisms, in contrast to the typically low tumor mutational burden of uveal melanoma.

Darovasertib-based combinations are being evaluated in HLA-A*02:01 negative patients, addressing a major unmet need in uveal melanoma therapy.

survival outcomes compared to historical benchmarks.[7,8]

Importantly, darovasertib-based combinations are being evaluated in HLA-A*02:01 negative patients, addressing a major unmet need in uveal melanoma therapy. The ongoing phase II/III DAR-UM-2 trial is expected to further define its role as a first-line treatment.[8]

These developments reflect a broader shift toward combination and biology-driven therapy, integrating targeted agents with immunotherapy and anti-angiogenic approaches.[7,8]

Emerging biomarkers and translational insights

- **Circulating tumor DNA**

Liquid biopsy techniques, particularly circulating tumor DNA (ctDNA), represent a significant advance in the management of uveal melanoma. ctDNA enables detection of minimal residual disease and may identify metastasis earlier than conventional imaging.[9]

This has important clinical implications, as early detection of metastasis may allow timely intervention and improved outcomes. Additionally, ctDNA offers a non-invasive method for monitoring treatment response, making it a valuable tool in both clinical practice and research settings.[9]

- **Aqueous humor and intraocular biomarkers**

Recent advances in intraocular fluid analysis have opened new avenues for understanding tumor biology. Studies led by Jesse L. Berry and colleagues have demonstrated that aqueous humor can serve as a surrogate for tumor biopsy, reflecting tumor-derived genetic alterations and disease dynamics.[10]

This approach provides a minimally invasive method for molecular profiling and offers insights into tumor evolution, particularly in intraocular malignancies. Although still evolving, aqueous humor analysis represents a promising addition to the growing field of liquid biopsy in ocular oncology.[10]

Contemporary clinical insights

Recent clinical data have highlighted that metastatic risk in uveal melanoma is dynamic rather than static. Conditional survival analyses suggest that patients who remain metastasis-free over time may experience improving prognosis, particularly in lower-risk groups.[3,4]

In parallel, combination therapy strategies are gaining attraction, including the integration of immunotherapy, targeted therapy, and liver-directed treatments. Early clinical studies suggest that such approaches may improve disease control compared to historical outcomes, although further validation is required.[7,8]

Advances in predictive modeling and large clinical datasets are also contributing to more individualized patient care. By integrating clinical, genetic, and biomarker data, clinicians are increasingly able to tailor surveillance and treatment strategies to each patient's unique risk profile.[1]

Conclusion

Uveal melanoma is undergoing a profound transformation. The integration of gene expression profiling, PRAME status, TCGA classification, and key mutations such as BAP1 and MBD4 has enabled more precise risk stratification and personalized care.[2-5]

The emergence of systemic therapies, particularly tebentafusp and darovasertib-based combinations, has expanded the therapeutic landscape and introduced

Advances in predictive modeling and large clinical datasets are also contributing to more individualized patient care.

the possibility of improving survival outcomes.[6-8] The growing emphasis on early systemic intervention and combination therapy reflects a shift toward proactive disease management.

At the same time, advances in biomarkers such as ct-DNA and aqueous humor analysis are redefining disease monitoring and paving the way for precision oncology.[9,10]

While challenges remain, the progress achieved in recent years marks a turning point. Uveal melanoma is no longer a static disease with limited options—it is an evolving field where biology-driven care is beginning to translate into meaningful clinical impact.

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Primary Vitreoretinal Lymphoma: *Evolving Concepts in Terminology, Pathobiology, Diagnosis, and Management*

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Primary vitreoretinal lymphoma (PVRL) is an uncommon lymphomatous proliferative disease of the vitreous, retina, and subretinal pigment epithelium. PVRL is largely a non-Hodgkin lymphoma of diffuse large B-cell origin. It typically manifests as a masquerade syndrome and is intimately linked to primary central nervous system lymphoma (PCNSL), which frequently results in a delayed or missed diagnosis.

Many aspects of PVRL remain debatable or poorly understood despite advancements in imaging and molecular diagnostics. The biological connection between ocular and central nervous system involvement, the best imaging techniques, difficulties in obtaining and interpreting biopsy samples, the changing role of local versus systemic therapy, and the proper terminology that distinguishes PVRL from other intraocular lymphomas are among them.

The objective of this review is to explore these important elements:

1. The idea of compartmental disease affecting the brain and eyes, and how it affects the course of the illness.

2. The justification for referring to PVRL rather than primary intraocular lymphoma.

3. The function of multimodal imaging includes the optical coherence

Contemporary classification distinguishes between primary vitreoretinal lymphoma (PVRL) and primary uveal lymphoma (PUL), based on anatomical origin and underlying biology.

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tomography benefits and drawbacks.

4. Current techniques for pathological diagnosis and biopsy.

5. Contemporary therapeutic approaches, including systemic therapy, intravitreal therapy, and recently created tailored therapeutics.

Early diagnosis, effective treatment, and better results in this difficult illness depend on a thorough grasp of these domains.

A. Terminology: Moving beyond primary intraocular lymphoma

The term primary intraocular lymphoma (PIOL) has historically been used to describe lymphomatous involvement confined to the eye; however, it encompasses biologically distinct entities with markedly different clinical behaviour. Contemporary classification distinguishes between primary vitreoretinal lymphoma (PVRL) and primary uveal lymphoma (PUL), based on anatomical origin and underlying biology.[1] This distinction is clinically critical, as it directly influences diagnostic evaluation, systemic work-up, and therapeutic approach.

PVRL is a subtype of non-Hodgkin lymphoma that is closely associated with primary central nervous system lymphoma (PCNSL) and most frequently diffuse large B-cell lymphoma (DLBCL).[1] It is characterized by aggressive behaviour and a strong tendency to involve the central nervous system. It mostly affects the vitreous, retina, and subretinal pigment epithelium. PVRL develops in immune-privileged areas and exhibits compartmental confinement rather than extensive systemic dissemination, unlike nodal lymphomas. The cancerous cells are usually of post-germinal center B-cell origin and often harbor mutations in CD79B and MYD88, which molecularly link them to PCNSL rather than systemic DLBCL.

Primary uveal lymphoma, on the other hand, is a distinct clinicopathological entity. It is most frequently a choroid-derived low-grade extranodal marginal zone lymphoma (MALT type).[1] In contrast to the vitreoretinal involvement shown in PVRL, it manifests clinically as an indolent, frequently unilateral process with little to no vitritis. CNS involvement is extremely rare, and systemic associations are uncommon. The disease usually progresses slowly, and localized treatments like external beam radiation are frequently used in place of systemic chemotherapy. This striking contrast encourages the adoption of more specific terms and highlights the shortcomings of the general term PIOL.

It is important to identify primary intraocular lymphomas from systemic lymphomas affecting the eye, which belong to a different category. Because of the choroid's strong vascular supply, it is typically the next sign of disseminated non-Hodgkin lymphoma. Systemic lymphomas, in contrast to PVRL, spread hematogenously and are linked to broad illness that necessitates systemic treatment. Understanding this distinction is crucial because ocular involvement in systemic lymphoma requires a fundamentally different therapy strategy and has significant prognostic implications.

B. Pathobiology and eye–CNS relationship

The best way to understand PVRL is as a component of the spectrum of primary central nervous system lymphoma (PCNSL), which affects immune-privileged areas such as the testes, brain, spinal cord, and eye.[2] Up to 90% of individuals eventually experience CNS involvement, and about 20% of patients have concomitant CNS disease.[1] PVRL exhibits compartmental progression as opposed to traditional metastasis, with a notable limitation to immune-privileged areas, in contrast to systemic lymphomas.

The cancerous cells are usually of post-germinal center B-cell origin and often harbor mutations in CD79B and MYD88, which molecularly link them to PCNSL rather than systemic DLBCL.

Up to 90% of individuals eventually experience CNS involvement, and about 20% of patients have concomitant CNS disease.

This can be explained by malignant B cells' ability to exploit the immunoevasive microenvironment of the eye and central nervous system, characterized by reduced antigen presentation, locally produced immunosuppressive cytokines, and restricted lymphatic drainage.

This selective involvement is explained by "homing of lymphoma cells" to the eye–CNS axis. In retinal and central nervous system tissues, malignant cells express chemokine receptors such as CXCR4 and CXCR5 that bind ligands such as CXCL12 and CXCL13 to enable directed migration. Additionally, adhesion molecules promote transmigration via the blood-brain and blood-retinal barriers. Recurrent genetic alterations, particularly mutations in MYD88 and CD79B, further improve survival signaling and microenvironmental adaptability. This coordinated homing and retention explains the normal clinical pattern of bilateral but asynchronous ocular involvement, recurrent CNS development despite local therapy, and infrequent systemic spread outside these compartments.

C. Clinical presentation

PVRL typically presents with an insidious onset, in sixth and seventh decade of life and frequently mimics chronic posterior uveitis.

- **Symptoms:**
  - — Blurred vision (most common)
  - — Floaters
  - — Mild ocular discomfort (occasionally)
  - — Photophobia (less common)

Owing to its disguise, a year-long delay in diagnosis is typical.[1]

- **Signs**
  - — ***Vitreous***
    - » Dense vitritis disproportionate to symptoms
    - » Clumped cells along vitreous fibrils ("aurora borealis")
    - » Transient response to corticosteroids
  - — ***Retina and subretinal space***
    - » Creamy yellow subretinal infiltrates
    - » Multifocal lesions with "leopard spot" appearance
    - » RPE changes and atrophy

D. Imaging in primary vitreoretinal lymphoma

Raising suspicion of PVRL, directing biopsies, and tracking treatment effectiveness, all depend on multimodal imaging. A combination of structural and functional imaging is needed to describe the disease because of its mask; no single modality is diagnostic.

- **Optical coherence tomography (OCT)**

In PVRL, OCT has become the most informative non-invasive imaging technique. It helps determine the degree of invasion by offering high-resolution cross-sectional imaging. OCT in PVRL typically has the following traits:

- — Sub-RPE hyperreflective nodular deposits
- — Hyperreflective subretinal infiltrates
- — Hyperreflective lesions inside the retina that affect both the inner and outer layers

Importantly, intraretinal involvement has been associated with a higher risk of CNS development, and sub-RPE deposits may be associated with disease recurrence. OCT is a crucial technique for monitoring therapeutic response.

Immunoglobulin heavy-chain rearrangement testing and MYD88 mutation analysis are two additional molecular tests that have greatly improved diagnostic sensitivity and are increasingly used in the routine assessment of suspected PVRL.

— RPE abnormalities and undulations

— Rarely associated with subretinal fluid

These findings demonstrate different degrees of lymphoma cell invasion in the retina. Importantly, intraretinal involvement has been associated with a higher risk of CNS development, and sub-RPE deposits may be associated with disease recurrence. OCT is a crucial technique for monitoring therapeutic response because regression of hyperreflective lesions shows how well a treatment is working.

- **Fundus autofluorescence (FAF)**

FAF can be used to understand RPE function and metabolic activity. While hypo-autofluorescent regions exhibit RPE shrinkage or disappearance, hyper-autofluorescent regions typically indicate stretched RPE or lipofuscin accumulation in active lesions in PVRL. OCT results closely resemble the patterns seen on FAF; it is a good tool for monitoring the course of the disease.

- **Fundus fluorescein angiography (FFA)**

FFA results are non-specific in PVRL. Hyperfluorescent window defects indicate RPE breakdown, whereas hypo fluorescent lesions are associated with regions of lymphomatous infiltration that block choroidal fluorescence. It is common to describe a "leopard spot" pattern that cycles between hypo- and hyperfluorescence. Significant vascular leakage is usually absent, unlike that seen in inflammatory uveitis, and may be a useful differentiator.

To demonstrate the range of distinctive findings across modalities, multimodal imaging is used to describe representative cases of primary vitreoretinal lymphoma. (Figures 1)

E. Biopsy and pathology

For individuals with steroid-resistant posterior uveitis, chronic vitritis, unusual subretinal infiltrates, or recurrent inflammation with equivocal tests, histopathological confirmation is still the gold standard for confirming PVRL. Prior to surgery, thorough collaboration with the ocular pathologist is essential since lymphoma cells are fragile and prone to rapid degeneration. A diagnostic pars plana vitrectomy is the most common procedure. Transport tubes, an infusion cannula, a syringe collection system, and a vitreous cutter should be part of a basic three-port vitrectomy setup. Before the infusion starts, undiluted vitreous should be obtained to improve cellular formation. Modest suction and modest cut rates (about 500–1000 cuts/min) are advised to preserve cellular shape and improve diagnostic accuracy.

To preserve cell viability for cytology and further analysis, the specimen should be transferred immediately into the appropriate medium, such as RPMI-1640 or cytolyt or absolute alcohol (70%), in accordance with institutional standards. Large atypical lymphoid cells with little cytoplasm, irregular nuclei, conspicuous nucleoli, and a high nuclear-to-cytoplasmic ratio in a necrotic backdrop are usually seen on cytological inspection. B-cell markers with a high Ki-67 proliferative index, such as CD20, CD19, and CD79a, are typically revealed by IHC. Immunoglobulin heavy-chain rearrangement testing and MYD88 mutation analysis are two additional molecular tests that have greatly improved diagnostic sensitivity and are increasingly used in the routine assessment of suspected PVRL.

It is still debatable whether patients with isolated ocular PVRL should get systemic medication. There is no conclusive proof of increased overall survival, although some research suggesting that early systemic treatment may slow the spread of CNS.

F. Treatment

Because of the compartmental character and substantial correlation with CNS disease, PVRL management is challenging. Treatment approaches can be broadly divided into two categories: systemic therapy and local (ocular) therapy. The choice is influenced by patient variables, CNS involvement, and disease severity.

- **Ocular (local) therapy**

Local therapy, which tries to reduce systemic toxicity and quickly control intraocular disease, is the cornerstone of treatment for isolated ocular disease.

— ***Intravitreal Methotrexate***

Intravitreal methotrexate (MTX) remains the most widely used and effective local therapy for PVRL. (Table 1)

High rates of local illness control and remission have been shown with this step-by-step approach. Relapses are frequent, though, and treatment-related side effects such as keratopathy, epitheliopathy, and a temporary rise in intraocular pressure may occur.

— ***Intravitreal rituximab***

An anti-CD20 monoclonal antibody called rituximab is being utilized more frequently, either alone or in conjunction with MTX.[5] It is very helpful in:

» MTX-intolerant patients

» Recurrent disease

» Combination regimens to reduce MTX toxicity

The standard dosage is 1 mg/0.1 mL at monthly intervals. Combination therapy is preferred because, although it is successful in managing vitreous disease, its penetration into sub-RPE lesions may be limited.

- **Systemic therapy**

Systemic therapy is indicated in:

» Concurrent CNS involvement

» High-risk ocular disease

» Few cases of bilateral or recurrent disease

— ***High-dose methotrexate-based regimens***

High-dose methotrexate (HD-MTX) forms the backbone of systemic therapy, similar to PCNSL protocols. Common regimens include:

» HD-MTX ± rituximab

» Combination regimens (e.g., MT-R protocol, CALGB-based regimens)

These therapies penetrate the blood–brain barrier and are effective in controlling CNS disease.

— ***Combination chemoimmunotherapy***

Regimens incorporating

» Methotrexate

» Rituximab

» Cytarabine or temozolomide

have been used, though toxicity remains a concern, especially in elderly patients.

Table 1: *Intravitreal methotrexate regimen for PVRL*

Induction	400 µg/0.1 mL	Twice weekly	4 weeks	Rapid control of active disease
Consolidation	400 µg/0.1 mL	Once weekly	8 weeks	Eliminate residual lymphoma cells
Maintenance	400 µg/0.1 mL	Once monthly	9–12 months	Prevent recurrence

- **Role of prophylactic systemic therapy**

It is still debatable whether patients with isolated ocular PVRL should get systemic medication. There is no conclusive proof of increased overall survival, although some research suggesting that early systemic treatment may slow the spread of CNS. As a result, treatment choices must to be customized according to patient characteristics and risk profiles.

- **Recent advances and emerging therapies**

Improved understanding of the molecular mechanisms in PVRL has led to a recent shift toward targeted, chemo-free regimens.[6]

— ***Immunomodulatory therapy***

» Lenalidomide + rituximab (R2 regimen).

» Phase II studies have demonstrated high response rates (~80–90%).

» Improved tolerability compared to traditional chemotherapy.

— ***Bruton tyrosine kinase (BTK) inhibitors***

» Agents such as zanubrutinib and ibrutinib target B-cell receptor signaling pathways.

» Particularly relevant in MYD88-mutated PVRL.

» Early studies show promising CNS and ocular responses.

— ***Chemo-free regimens***

Recent prospective studies combining:

» Rituximab

» Lenalidomide

» BTK inhibitors

have demonstrated high remission rates with reduced systemic toxicity, representing a paradigm shift in management.[7]

- **Consolidation and advanced therapies**

» Whole-brain radiotherapy (WBRT): Reserved for refractory or relapsed CNS disease.

» Autologous stem cell transplantation: Considered in selected younger patients with aggressive or recurrent disease.

G. Prognosis

Despite advances in therapy:

- 65–90% develop CNS involvement.
- Recurrence (both ocular and CNS) is common.
- Survival is largely determined by CNS disease.

Conclusion

A strong index of suspicion is necessary for the diagnosis of PVRL, a unique neuro-ophthalmic cancer. A switch from PIOL to PVRL reflects a better comprehension of its biology and clinical behaviour. Although local disease control has improved with advances in imaging and targeted therapy, CNS progression remains the primary challenge. Future studies should focus on methods to improve long-term survival and prevent/delay CNS involvement.

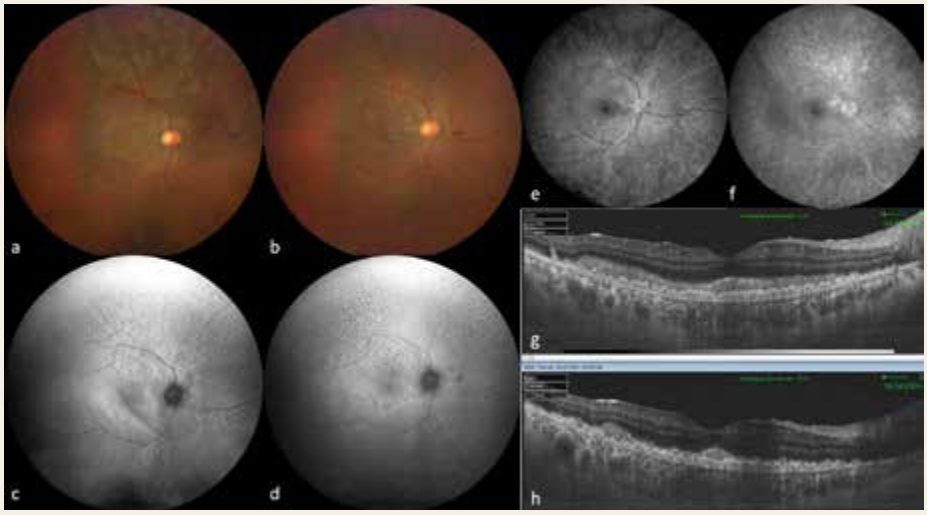

Figure 1: *Multimodal imaging findings in a representative case of primary vitreoretinal lymphoma (PVRL). (a) Baseline color fundus photograph of the right eye demonstrating multiple subtle creamy-yellow subretinal infiltrates at the posterior pole, consistent with sub-retinal pigment epithelium (sub-RPE) lymphomatous deposits, with associated mild vitreous haze. (b) Color fundus photograph following two intravitreal methotrexate injections showing partial resolution of vitreous membranes and subretinal deposits. (c, d) Corresponding fundus autofluorescence (FAF) images demonstrating a granular pattern of mixed hyperautofluorescent and hypoautofluorescent lesions, corresponding to areas of active sub-RPE infiltration and retinal pigment epithelium (RPE) disturbance. (e, f) Fundus fluorescein angiography (FFA) in the arterial and arteriovenous phases, respectively, revealing multiple punctate hypofluorescent lesions with surrounding granular hyperfluorescence, producing the characteristic "leopard-spot" appearance due to blockage from infiltrates and window defects secondary to RPE alteration. (g) Baseline swept-source optical coherence tomography (OCT) showing diffuse hyperreflective sub-RPE deposits with irregular RPE undulations and focal disruption of the outer retinal architecture, characteristic of PVRL infiltration. (h) Follow-up OCT after initiation of treatment demonstrating partial regression of sub-RPE deposits and improvement in RPE contour, highlighting early structural response to therapy.*

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Recent Advances in Retinal and Choroidal Tumours

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The landscape of retinal and choroidal tumour management has been transformed by multimodal imaging, precision pharmacology, and genomically informed surgery. Across six distinct entities — choroidal osteoma, retinoblastoma, uveal melanoma, retinal capillary haemangioblastoma, circumscribed choroidal haemangioma, and vasoproliferative tumours — the shift from passive observation to targeted, compartment-specific intervention is now firmly established.

Choroidal osteoma

A landmark case report demonstrated that anti-osteoclastic therapy — bisphosphonates (oral alendronate) and RANKL inhibitors (denosumab) — can stabilise choroidal osteoma progression over nine years by preventing tumour decalcification and subsequent outer retinal atrophy. Enhanced depth imaging OCT now visualises the characteristic sponge-like deossified tissue, enabling precise treatment monitoring. Anti-VEGF therapy effectively manages secondary choroidal neovascularisation.

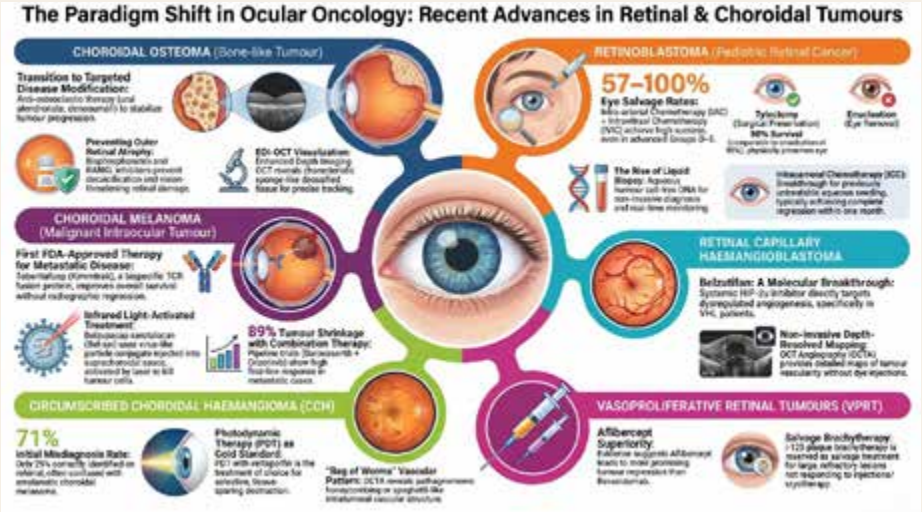
Retinoblastoma

Intra-arterial chemotherapy (IAC) has transformed outcomes in advanced retinoblastoma (Groups D–E), delivering high-dose melphalan directly to the ophthalmic artery with reduced systemic toxicity. Combined IAC and intravitreal chemotherapy (IViC) achieves eye salvage rates of 57–100% depending on tumour group. Intravitreal topotecan has emerged as a safer alternative to melphalan, demonstrating zero retinal toxicity and 100% eye salvage in early studies, effectively controlling vitreous seeding — historically the hardest compartment to treat.

Intracameral chemotherapy (ICC)

Anti-osteoclastic therapy — bisphosphonates (oral alendronate) and RANKL inhibitors (denosumab) — can stabilise choroidal osteoma progression over nine years by preventing tumour decalcification and subsequent outer retinal atrophy.

addresses previously untreatable aqueous seeding, achieving complete regression in most cases within one month. A landmark 2024 JAMA randomised trial confirmed that 3 cycles of CEV chemotherapy produce equivalent 5-year disease-free survival to 6 cycles, significantly reducing treatment burden in high-risk unilateral retinoblastoma.



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Prognostic biomarkers under investigation — including microRNA, cone-rod homeobox (CRX) transcriptors, and CTX mRNA — may allow earlier identification of high-risk patients. Liquid biopsy using aqueous humour cell-free DNA enables non-invasive diagnosis, real-time treatment monitoring, and recurrence detection, with serial somatic copy number alterations correlating with tumour regression and relapse.

Immunotherapy shows early promise in metastatic disease — GPC2-targeted CAR-T cells and anti-GD2 monoclonal antibodies (naxitamab, dinutuximab beta) have achieved sustained remissions exceeding 4 years in select CNS-metastatic cases. Tylectomy offers surgical eye-preserving resection with 96% survival, comparable to enucleation (95%) and superior to eye salvage without resection (90%). The chemoplaque — an episcleral device providing sustained intravitreal topotecan release — is currently in Phase I evaluation (STEP-RB). VCN-01, an oncolytic adenovirus targeting the RB1 pathway, is administered intravenously to prevent brain metastasis, representing a novel virotherapy frontier in high-risk disease.

Choroidal melanoma

For primary disease, belzupacap sarotalocan (bel-sar / AU-011) — a virus-like particle drug conjugate activated by infrared light via suprachoroidal injection — is under Phase 2b/3 investigation, selectively targeting tumour cells through modified heparan sulphate proteoglycans and inducing long-term antitumour immunity. Prophylactic anti-VEGF therapy for radiation retinopathy is being prospectively evaluated in the DRCR Protocol AL study.

The landmark breakthrough in metastatic disease is tebentafusp (Kimmtrak) — the first FDA-approved therapy for metastatic uveal melanoma (2022). This bispecific TCR/anti-CD3 fusion protein redirects T cells against gp100-expressing tumour cells, demonstrating improved overall survival even without radiographic tumour regression. Early ctDNA clearance has emerged as a promising surrogate

Tebentafusp — the first FDA-approved therapy for metastatic uveal melanoma — improves survival even without radiographic regression.

Belzutifan, a systemic HIF-2α inhibitor, represents the most significant therapeutic advance — directly targeting dysregulated angiogenesis in VHL-associated disease and achieving meaningful lesion stabilisation.

biomarker of treatment response.

In the pipeline, darovasertib (PKC inhibitor) combined with crizotinib has shown 89% tumour shrinkage and a 50% first-line response rate in metastatic disease. The nivolumab plus relatlimab (LAG-3 blockade) combination is under trial given higher LAG-3 expression in uveal melanoma versus PD-1/PD-L1. Adjuvant sunitinib shows early promise in reducing metastatic risk. Genetic profiling via DecisionDx-UM (Class 1 vs Class 2) now guides surveillance intensity and adjuvant trial eligibility — heralding a personalised approach to this historically undertreated malignancy.

Retinal capillary haemangioblastoma

OCT angiography now enables non-invasive, depth-resolved tumour mapping, revolutionising diagnosis and treatment monitoring. Belzutifan, a systemic HIF-2α inhibitor, represents the most significant therapeutic advance — directly targeting dysregulated angiogenesis in VHL-associated disease and achieving meaningful lesion stabilisation. Pre-operative intravitreal anti-VEGF agents have improved surgical safety by reducing tumour vascularity, contributing to vitreoretinal reattachment rates exceeding 80% in complex cases. Next-generation sequencing has enhanced mosaicism detection, refining genetic counselling and enabling earlier systemic surveillance — shifting management from reactive intervention toward proactive, molecularly informed care.

Circumscribed choroidal haemangioma

CCH is a rare, benign vascular hamartoma that nonetheless causes serious visual impairment in over half of patients through subretinal fluid, serous retinal detachment, retinoschisis, and neovascular glaucoma. Diagnosis remains notoriously difficult — only 29% of cases are correctly identified on referral, with frequent confusion with amelanotic choroidal melanoma.

Multimodal imaging has transformed diagnosis: ICGA with its pathognomonic late-phase washout remains the gold standard. EDI-OCT outperforms ultrasound for thin lesions, while OCTA non-invasively reveals characteristic "bag of worms" or "spaghetti-like" intratumoral vascular patterns. Swept-source OCTA adds deeper penetration with a distinctive honeycombing pattern. Photodynamic therapy (PDT) with verteporfin is now the treatment of choice, with double-dose, double-fluence, and half-fluence refinements improving outcomes by lesion location and size. Anti-VEGF agents manage macular oedema but require combination with PDT for meaningful structural benefit. Proton beam therapy offers durable control for large tumours (>3 mm) or PDT failures.

Vasoproliferative retinal tumours

VPRTs are rare benign peripheral retinal lesions with no standardised treatment. Wide-field imaging and swept-source OCTA enable non-invasive tumour characterisation. Aflibercept has shown more promising tumour regression than bevacizumab. Intravitreal dexamethasone implants are increasingly used as adjuncts for severe exudation. Growing evidence supports PPV with cryotherapy or endoresection for vision-threatening complications. I-125 plaque brachytherapy serves as salvage for large refractory lesions. Multimodal, individualised therapy remains the standard; long-term surveillance is essential given the propensity for recurrence, macular oedema, and epiretinal membrane formation.

Conclusion

The evolving landscape of retinal and choroidal tumours reflects a clear

Wide-field imaging and swept-source OCTA enable non-invasive tumour characterisation. Aflibercept has shown more promising tumour regression than bevacizumab.

shift from reactive management to precision-based, compartment-specific care. Advances in molecular profiling, liquid biopsy, targeted therapies, and high-resolution imaging have improved diagnosis and now allow real-time monitoring and individualized treatment. Together, these developments have moved the goal from simply controlling the tumour to preserving vision and improving long-term systemic outcomes. Emerging biomarkers and targeted agents are also linking ocular disease with systemic oncology, helping refine follow-up and treatment strategies. As these advances continue to develop, integrating genomics, imaging, and therapy into a patient-centered approach will enable earlier intervention, reduce morbidity, and ensure better visual outcomes along with improved survival.

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Recent Advances in Diagnosis and Management of Periocular and Ocular Surface Tumours

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Introduction

Periocular and ocular surface tumors comprise a heterogeneous group of benign and malignant neoplasms arising from the eyelids, conjunctiva, cornea, and adjacent adnexal structures. Common malignancies include basal cell carcinoma (BCC), sebaceous gland carcinoma (SGC), conjunctival melanoma, melanoma of the eyelid, ocular surface squamous neoplasia (OSSN), and ocular adnexal lymphomas.

Traditionally, diagnosis has relied on detailed history for risk factor assessment and clinical examination supplemented by slit-lamp bio-microscopy, incisional or excisional biopsy and histopathological evaluation as the gold standard. Management has predominantly involved surgical excision with margin control, often combined with cryotherapy, radiotherapy, or topical chemotherapeutic agents such as neoadjuvant or adjuvant treatment modalities.

Recent years have witnessed substantial advances in both diagnosis and management of periocular and ocular surface tumors. High-resolution imaging modalities including anterior segment optical coherence tomography (AS-OCT), ultrasound bio-microscopy (UBM), and in vivo confocal microscopy have enabled improved non-invasive tumor characterization. American Joint

High-frequency ultrasound (HFUS) is being investigated to provide non-invasive in vivo delineation of periocular lesions, permitting assessment of dimensions, morphology, and tumor volume.

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Committee on Cancer Classification -8 (AJCC-8) molecular diagnostics, immunohistochemistry, targeted therapies, and emerging artificial intelligence–based diagnostic tools are increasingly re-defining tumor detection, classification, and prognostication. Parallel advances in tissue-sparing surgery, topical and immunomodulatory therapies have shifted management paradigms toward individualized, vision-preserving modalities.

Basal cell carcinoma (BCC)

Basal cell carcinoma (BCC) is the most common malignant eyelid tumor globally. With technology on the rise, for diagnostics, high-frequency ultrasound (HFUS) is being investigated to provide non-invasive in vivo delineation of periocular lesions, permitting assessment of dimensions, morphology, and tumor volume, and ex vivo use of HFUS in assessment of tumor margins may enhance tumor margin evaluation after excision increasing confidence of tumor free margins after excision.[2] Also, reflectance confocal microscopy, a non-invasive, real-time cellular imaging that facilitates differentiation of malignant from benign eyelid lesions, that refines indications for surgical excision versus conservative observation and structured follow-up, is also being studied.[2]

Traditionally, the management strategy for BCC encompasses surgical biopsy which is either incisional or excisional. When imaging-Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) demonstrates intraocular or orbital extension, globe-sacrificing procedures such as enucleation or orbital exenteration may be warranted respectfully to achieve oncologic control.

Advances in margin-controlled histopathological assessment have refined the surgical management of BCC. Standard frozen-section control enables intraoperative microscopic evaluation of excised tumor margins from the surgical bed, permitting confirmation of tumor-free margins and facilitating immediate/same day periocular reconstruction; adjunctive double freeze–thaw cryotherapy to the peripheral margins is often employed to eradicate residual microscopic disease.[1] Frozen section has evolved and clenched its niche as an indispensable tool and technique with a sensitivity and specificity of 100% and 93.1% respectively and has revolutionized management of periocular tumors.[2]

Mohs Micrographic Surgery (MMS) and other techniques of Peripheral and Deep En- face Margin Assessment (PDEMA) represent tissue-sparing approaches wherein only the primary lesion is excised, followed by sequential removal of thin tissue layers from the tumor bed for en-face histological examination until clear margins are achieved. This strategy optimizes oncologic clearance while minimizing defect size and preserving maximal periocular tissue essential for functional and aesthetic eyelid reconstruction. [3]

Traditionally, radiotherapy has served as a primary modality in patients unfit for surgery or where anticipated postoperative functional morbidity is significant, and as an adjuvant option for residual disease or tumors abutting vital structures such as the lacrimal drainage apparatus.[1] However, conventional radiotherapy is associated with higher recurrence rates, difficulty in early detection of recurrence, and an increased risk of secondary cutaneous malignancies. Contemporary practice favors targeted techniques, including electron beam therapy with ocular shielding and Intensity-Modulated Radiotherapy (IMRT), which limit tissue penetration and reduce collateral ocular toxicity such as keratitis and cataract,

Frozen section has evolved and clenched its niche as an indispensable tool and technique with a sensitivity and specificity of 100% and 93.1% respectively and has revolutionized management of periocular tumors.

Immunotherapy with the (Program Death -1) PD-1 inhibitor cemiplimab has emerged as an effective second-line option for advanced BCC.

thereby enhancing organ preservation while maintaining oncologic control.[3]

Systemic therapy has significantly expanded the therapeutic armamentarium for advanced BCC. Hedgehog pathway inhibitors, including vismodegib and sonidegib, have transformed the management of locally advanced, metastatic, recurrent, or surgically and radio therapeutically ineligible BCC by targeting aberrant Hedgehog signaling.[1,4] (Figure 1) Despite their efficacy, long-term adherence is often limited by cost and adverse effects such as muscle spasms, alopecia, dysgeusia, and teratogenicity.[1] More recently, immunotherapy with the (Program Death -1) PD-1 inhibitor cemiplimab has emerged as an effective second-line option for advanced BCC, particularly in tumors demonstrating resistance or intolerance to Hedgehog pathway inhibitors, thereby offering durable responses in otherwise refractory disease.

Artificial intelligence (AI) with respect to BCC is an emerging yet largely investigational adjunct requiring validation through robust multicentric datasets. Current research explores automated lesion detection from clinical images, risk stratification based on morphological tumor features, and predictive modelling for surgical margin status and recurrence risk. A deep learning model applied to whole slide images (stained with hematoxylin and eosin) accurately differentiated eyelid basal cell carcinoma and sebaceous carcinoma with 98.3% accuracy.[5] These tools aim to enhance diagnostic precision, guide preoperative planning, and enable individualized surveillance.[6]

Squamous cell carcinoma (SCC)

Periocular SCC is the second most common malignant eyelid tumor after BCC and demonstrates a more aggressive biological behavior, with a greater propensity for local invasion, perineural spread, regional lymph node metastasis but rarely, distant dissemination.

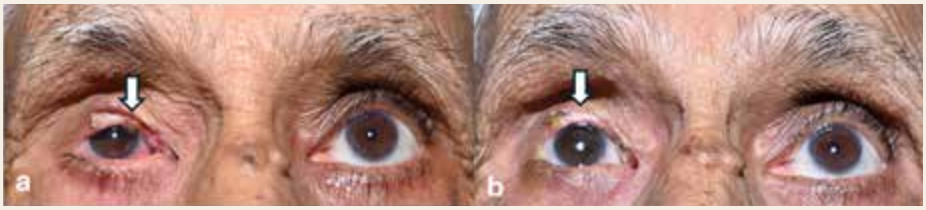

Figure 1: *External photo of a Right eye upper eyelid sclerosing Basal cell carcinoma showing multiple nodularity, loss of eyelid margin contour and madarosis (shown with the arrow), ulcerative lid margin lesion with rolled edges (fig 1a).An external photo showing reduction in tumor thickness after 1 month of vismodegib therapy (fig 1b).*

Targeted systemic therapy with epidermal growth factor receptor inhibitors, such as cetuximab, has been employed in advanced disease unsuitable for immunotherapy. Concurrent chemoradiation is an evolving modality, particularly for patients with nodal involvement who are poor surgical candidates or in the adjuvant setting for residual disease and extracapsular extension, potentially reducing the need for orbital exenteration. Overall, recent therapeutic advances in SCC broadly parallel those established for BCC, with an increasing emphasis on multimodal, globe-sparing strategies.

Neoadjuvant chemotherapy (NACT) has a potential role in downstaging locally advanced eyelid squamous cell carcinoma with orbital extension, thereby enabling less mutilating surgical intervention with the possibility of globe preservation and better aesthetic outcomes, without compromising oncologic principles.

Although direct evidence in eyelid SCC remains limited, this strategy is extrapolated from conjunctival SCC and eyelid sebaceous gland carcinoma with orbital invasion, wherein platinum-based NACT has demonstrated significant tumor regression, facilitating conversion of exenteration-requiring disease to more conservatively resectable or treatable state.[7]

The demonstration of androgen receptor expression in a subset of SGC has prompted investigational use of anti-androgen targeted therapies in advanced disease, reflecting a growing shift toward personalized, biomarker-driven oncologic management.

Sebaceous gland carcinoma (SGC)

In contrast to the predominance of BCC with respect to periocular malignancies in Caucasian populations, SGC represents the most common malignant eyelid tumor in several Asian and Indian cohorts, reflecting distinct epidemiologic patterns.[8]

Conjunctival map biopsies constitute an essential component of staging, enabling detection of pagetoid intraepithelial spread and guiding the extent of surgical management. Systemic therapeutic approaches are evolving for advanced disease. Platinum-based neoadjuvant chemotherapy has been utilized in locally advanced or metastatic SGC to achieve tumor downstaging prior to definitive surgical management.[7] In parallel, immunotherapeutic strategies analogous to those employed in advanced BCC and SCC, particularly immune checkpoint inhibition, are being explored in refractory or unresectable cases. Additionally, the demonstration of androgen receptor expression in a subset of SGC has prompted investigational use of anti-androgen targeted therapies in advanced disease, reflecting a growing shift toward personalized, biomarker-driven oncologic management.

Recent advances in the management of SGC have increasingly incorporated immunohistochemical and molecular profiling to improve diagnostic precision and therapeutic stratification. Immunohistochemical markers, including adipophilin, androgen receptor (AR), epithelial membrane antigen (EMA), and Ber-EP4, enhance diagnostic accuracy and facilitate differentiation of SGC from basal cell carcinoma and squamous cell carcinoma, particularly in poorly differentiated or ambiguous lesions. Concurrently, molecular studies have identified alterations such as p53 mutations and mismatch repair deficiency, with recognized associations with Muir–Torre syndrome, thereby underscoring the need for systemic evaluation and genetic counselling in selected patients with suggestive clinical or familial features.[9]

Pertaining to SGC and AI, exploratory tools for early diagnosis and prognostication of periocular SGC include automated differentiation of eyelid SGC from clinical and dermoscopic images via deep learning algorithms as machine learning–assisted digital pathology recognizes lipid-rich tumor cells and subtle sebaceous differentiation.[6]

Ocular surface squamous neoplasia (OSSN)

OSSN is a unifying term encompassing the full spectrum of conjunctival squamous epithelial tumors, ranging from conjunctival intraepithelial neoplasia (CIN) to invasive squamous cell carcinoma.[9,10] Traditionally, the diagnosis of OSSN has relied predominantly on careful slit-lamp biomicroscopy, which facilitates recognition of characteristic morphological patterns such as leukoplakic, papilliform or placoid lesions, as well as assessment of tumor mobility and staining characteristics, particularly positivity with Rose Bengal dye.[11]

Recent strides made in the diagnosis of OSSN include high-resolution, non-invasive imaging modalities such as AS-OCT which facilitates differentiation of OSSN from benign conjunctival subepithelial lesions such as pterygium

Plaque brachytherapy has emerged as an important globe-salvaging modality, particularly for residual post-surgical disease, recurrent OSSN, focal scleral invasion, and diffuse lesions not amenable to wide local excision or refractory to topical chemotherapy.

and pingueculum by demonstrating an abrupt transition from normal epithelium to a thickened, hyperreflective epithelial layer with variable posterior shadowing depending on keratin content; it also assists in distinguishing OSSN from other ocular surface diseases such as pterygium and malignancies such as conjunctival lymphoma.[12,13]

Studies have shown that the specificity and sensitivity of AS-OCT in diagnosing OSSN is on the high side, with one study revealing about 94.7% specificity and 100% sensitivity.[14]

In vivo confocal microscopy provides quasi-histological visualization, revealing pleomorphic hyperreflective epithelial cells with increased nuclear-to-cytoplasmic ratio, supporting early diagnosis and delineation of tumor margins.[15,16] Ultrasound biomicroscopy (UBM), using high-frequency ultrasound, enables assessment of tumor depth and detection of scleral or intraocular extension, thereby guiding tailored management strategies.

Plaque brachytherapy has emerged as an important globe-salvaging modality, particularly for residual post-surgical disease, recurrent OSSN, focal scleral invasion, and diffuse lesions not amenable to wide local excision or refractory to topical chemotherapy.[17] This modality is often employed as part of multimodal therapy, either adjunctive to chemoreduction or following tumor debulking in the absence of intraocular or intraorbital extension and has demonstrated favorable outcomes in the management of advanced ocular surface squamous neoplasia; a large series utilizing Ruthenium-106 reported complete tumor regression and 100% globe salvage, with recurrence rates of approximately 5% over a three-year follow-up. Additional studies corroborate high globe preservation rates approaching 100% and low recurrence rates (<10–27%), underscoring its efficacy in invasive disease.[13]

Systemic neoadjuvant chemotherapy is used in OSSN when local modalities alone are unlikely to achieve adequate tumor control, such as extensive, diffuse or fungating lesions not amenable to primary excision. This approach aims to reduce tumor bulk, vascularity, limit subclinical spread and thereby convert unresectable or exenteration-requiring tumors into lesions suitable for globe-sparing surgery.[13] (Figure 2) Although no standardized regimen exists, protocols extrapolated from head and neck squamous cell carcinoma commonly employ platinum-based agents (cisplatin or carboplatin) combined with 5-fluorouracil and with taxanes (docetaxel or paclitaxel) added for aggressive disease.[13] Early experiences

Figure 2: *Neoadjuvant chemotherapy for extensive conjunctival SCC. External photographs showing the pre-systemic chemotherapy extensive ossn with orbiral extension and loss of globe details (Fig 2a). Appearance after 3 cycles of systemic chemotherapy (paclitaxel and cisplatin) showing significant reduction of tumor bulk, making globe structures visible.*

Immune checkpoint inhibitors targeting PD-1 and CTLA-4 pathways have demonstrated efficacy in metastatic conjunctival and periocular melanoma.

Emerging applications of artificial intelligence in digital histopathology and ocular imaging aim to automate lymphoid cell classification, distinguish reactive hyperplasia, and improve early detection and staging accuracy.

with systemic PD-1 inhibitors have also demonstrated promising neoadjuvant responses and being investigated for OSSN.[13]

In the molecular understanding of OSSN pathogenesis, ultraviolet-induced DNA damage, human papillomavirus–associated oncogenesis, angiogenic and immune dysregulation have stimulated investigation into targeted and adjunctive therapies.[18] These include antiviral agents such as cidofovir, anti-VEGF agents (bevacizumab), retinoids (topical vitamin A derivatives), and immunomodulatory approaches including checkpoint inhibition.[15] While these modalities remain investigational and are primarily considered in refractory, HPV-associated, or highly vascular tumors, their adoption as standard of care is limited by the paucity of robust prospective evidence.[15]

With AI and OSSN, deep learning–based analysis of slit-lamp photographs and AS-OCT are demonstrating potential for early detection, automated tumor delineation, prediction of recurrence and monitoring of treatment response.[16] Futuristic AI-driven predictive models are underway which can identify lesions best suited for surgical versus topical or systemic therapy.

Melanoma

Periocular and conjunctival melanomas are uncommon yet aggressive melanocytic malignancies. Advances in diagnostic and therapeutic strategies have significantly refined contemporary management. High-resolution AS-OCT, UBM and orbital MRI facilitate accurate delineation of tumor margins and adjacent structural involvement, thereby optimizing surgical planning and radiotherapeutic dosing.[19] Enhanced "no-touch" biopsy techniques, together with confocal microscopy and dermoscopy, provide improved non-invasive cellular-level assessment. Globe-sparing surgical approaches, including limbal stem cell transplantation have improved functional outcomes while maintaining oncologic safety. Molecular profiling has identified actionable mutations such as BRAF, NRAS, NF1, and TERT, enabling targeted therapy with BRAF and MEK inhibitors in advanced disease.

Immune checkpoint inhibitors targeting PD-1 and CTLA-4 pathways have demonstrated efficacy in metastatic conjunctival and periocular melanoma, paralleling treatment paradigms in cutaneous melanoma.[1] Modern radiation modalities including surface brachytherapy, electron beam therapy, and plaque brachytherapy offer effective local control for invasive disease with scleral involvement or microscopic residual tumour while minimizing collateral ocular toxicity.[19]

Adjunctive therapies such as topical imiquimod, cytokine-based agents including interleukin-2 and pegylated interferon-α2b, and oncolytic virus therapy with talimogene laherparepvec are being explored for unresectable or recurrent disease, reflecting a shift toward multimodal, personalized oncologic care.[1]

Conjunctival lymphoma

Conjunctival lymphoma, most commonly extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), represents the predominant ocular surface lymphoproliferative malignancy and typically manifests as a painless "salmon-patch" subconjunctival lesion.[1]

Historically, treatment is stage-adapted: localized conjunctival lymphoma is effectively managed with low-dose external beam radiotherapy, whereas systemic disease warrants chemotherapy (e.g., CHOP-based regimens) under

hemato-oncology protocols.[20] Indolent, asymptomatic MALT lymphomas in elderly or stable localized cases may be observed.

Molecular and cytogenetic profiling, including translocations such as t (11;18) (q21;q21), assists in subclassification, prognosis and therapeutic selection.[21] Contemporary advances include CD20-targeted therapy with rituximab, either as monotherapy or combined with chemotherapy, for bulky or orbital disease, while conformal and ultra-low-dose radiotherapy reduce ocular toxicity.[21] Emerging applications of artificial intelligence in digital histopathology and ocular imaging aim to automate lymphoid cell classification, distinguish reactive hyperplasia, and improve early detection and staging accuracy.[20]

Conclusion

The evolution of diagnostics and management of periocular tumours and OSSN has transformed ocular oncology from an era dominated by radical ablative procedures to one centered on precision and globe-sparing care. Advances in high-resolution imaging, minimally invasive biopsy, targeted topical and systemic therapies, refined surgical techniques, and precision radiotherapy now enable earlier diagnosis, accurate staging, and tailored treatment. These developments align with the core principles of ocular oncology: save life, salvage the globe and salvage vision; demonstrating that effective oncologic control can increasingly be achieved while preserving ocular integrity and functional vision.

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Targeted Therapy in Ocular Oncology: *A Comprehensive Review*

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Introduction

Eye cancers, including periocular basal cell carcinoma (BCC), squamous cell carcinoma (SCC), ocular adnexal lymphoma (OAL), conjunctival melanoma (CoM), and uveal melanoma (UM), represent a diverse group with unique molecular drivers receptive to targeted treatment.[1,2] Unlike traditional chemotherapy, targeted agents and immunotherapy focus on specific oncogenic pathways or stimulate the immune system to kill tumours. This review highlights mechanisms, clinical effectiveness, side effects, and future directions for these types of tumours.

Periocular basal cell carcinoma

BCC makes up 75–90% of skin cancers and about 90% of eyelid cancers.[1] Advanced periocular BCC (AJCC T4) often requires orbital exenteration. The main oncogenic factor is the dysregulation of the Sonic Hedgehog (SHH) pathway due to PTCH1 loss in 70% of cases or activating mutations in SMO in 20% of cases, with TP53 mutations found in 44–100%. [1,3]

Vismodegib (150 mg taken daily), approved by the FDA in 2012, is the first SMO inhibitor.[3] In one of the largest periocular studies (n=21), complete and partial response rates were each 48%. In another cohort of 384 patients, the ORR was 75%, and orbital exenteration rates dropped from 46% to 10% (P=0.016).[1,6] However, around 20% of these patients develop resistance, often due to SMO mutations or Ras/MAPK pathway activation.

Sonidegib (200 mg taken daily), approved in 2015, achieves ORRs of 47–61%, with a quicker time to response than vismodegib (median 2.5 vs. 4.7 months).[4] Common side effects include taste changes (30–100%), muscle spasms

Sonidegib (200 mg taken daily), approved in 2015, achieves ORRs of 47–61%, with a quicker time to response than vismodegib (median 2.5 vs. 4.7 months).

Immune checkpoint inhibitors like cemiplimab and pembrolizumab achieve ORRs of 44–50% in cutaneous SCC. In cases of conjunctival SCC with orbital extension and high tumour mutational burden complete responses happened in 4 out of 5 patients.

(15–100%), hair loss (47–75%), and weight loss (23–83%); grade 3–4 toxicity occurs in about 8–10%.[1,3,4] New strategies such as imiquimod 5% for superficial lesions and intermittent dosing of vismodegib are emerging for resistance management.[1]

Periocular squamous cell carcinoma

SCC represents 5–10% of periocular cancers. The primary targets for therapy are EGFR overexpression (77%) and PD-L1 expression (47% overall, increasing to 79% in T3/T4 disease). [1,7]

Immune checkpoint inhibitors like cemiplimab and pembrolizumab achieve ORRs of 44–50% in cutaneous SCC.[1,7] In cases of conjunctival SCC with orbital extension and high tumour mutational burden (>60 mut/Mb), complete responses happened in 4 out of 5 patients. Grade 3–4 toxicities include high blood pressure and the rare occurrence of Vogt-Koyanagi-Harada-like uveitis. [7]

EGFR inhibitors, such as cetuximab combined with radiotherapy, extend median OS to 24.4 months compared to 14.9 months with radiotherapy alone.[1,2] Erlotinib and gefitinib yield 2-year OS rates of 65% and 72%, respectively, with ocular side effects that include excessive eyelashes, corneal erosion, and eyelid inflammation. [1,2]

Ocular adnexal lymphoma

OAL accounts for 5–10% of extranodal lymphomas, with EMZL being the most common subtype.[15] Over 90% of B-cell lymphomas express CD20, which makes them targets for rituximab.[1,15]

Systemic rituximab (375 mg/m² weekly for 4–6 weeks) has ORRs of 62–100%.[1,15] When combined with chlorambucil in EMZL, it improves 5-year OS (68% vs 51%) and ORR (95% vs 86%) compared to rituximab alone.[15] The R-CHOP regimen for DLBCL/MCL achieves a 10-year disease-specific survival rate of 96% in stage IVE EMZL.[1,15]

Intralesional rituximab (subconjunctival 10–20 mg/mL) achieves complete response in 73% and partial response in 27% at a mean follow-up of 37 months, with only short-term local side effects.[8] IFN-alpha-2B provides an 85% 5-year progression-free survival in EMZL, while radioimmunotherapy with yttrium-90-labelled ibritumomab leads to complete remission in 83% of patients at 3 months.[1,2]

Conjunctival melanoma

CoM has an incidence of 0.2–0.7 per million but carries a 5-year local recurrence rate of 36–45% and a 10-year metastasis risk of 19%.[14] BRAF V600E mutations are present in 40%, PD-L1 is seen in 19% of tumour cells, and TERT mutations affect 32–43%.[14]

BRAF/MEK inhibitors: Vemurafenib alone achieved sustained complete remission for 3 years in a metastatic CoM case.[14] Dabrafenib combined with trametinib resulted in significant tumour size reductions in several cases, with side effects including fever, sensitivity to light, and serous retinopathy (4% for vemurafenib and 27% for cobimetinib combinations).[14,16]

Immune checkpoint inhibitors are the recommended first-line treatment for metastatic CoM. Nivolumab alone resulted in complete remission in all 5 patients in one series (follow-up 1–36 months).[13] The combination of ipilimumab and nivolumab improves response rates but comes with higher risks of severe side effects (59%).[13,14] Clinicians should be aware of pseudoprogression to prevent premature treatment stops.[1,14]

Uveal melanoma

UM is the most common primary eye

IFN-alpha-2B provides an 85% 5-year progression-free survival in EMZL, while radioimmunotherapy with yttrium-90-labelled ibritumomab leads to complete remission in 83% of patients at 3 months.

The low tumour mutational burden and an immunosuppressive environment make UM largely resistant to standard immune checkpoint inhibitors.

cancer in adults. Metastases occur in 45% of cases within 15 years (90% in the liver), with a median OS of 10–12 months for metastatic disease.[1,9,18] GNAQ/GNA11 mutations (~90%) activate PKC/MAPK/PI3K signaling; loss of BAP1 (47%) indicates a worse outlook.[1,11] The low tumour mutational burden and an immunosuppressive environment make UM largely resistant to standard immune checkpoint inhibitors.[9,18]

Immune checkpoint inhibitors in metastatic UM: Nivolumab, pembrolizumab, and atezolizumab give ORRs of only 3.6–17% and median OS of 4.6–20 months.[1,9,18] The combination of ipilimumab and nivolumab offers the best responses (ORR 12–17%, median OS 12.7–19.1 months) but is still much less effective than in cutaneous melanoma.[9,18]

Table 1: *Key targeted agents, mechanisms, regulatory status, and adverse effects*

Drug	Tumour Type	Mechanism	FDA Status	Key Adverse Effects
Vismodegib	Periocular BCC	SMO inhibitor (SHH)	Approved 2012	Dysgeusia, muscle spasm, alopecia
Sonidegib	Periocular BCC	SMO inhibitor (SHH)	Approved 2015	Muscle cramps, elevated CK
Cemiplimab	SCC, BCC	Anti-PD-1 mAb	Approved 2018	Colitis, dermatitis, pneumonitis
Pembrolizumab	SCC, melanoma	Anti-PD-1 mAb	Approved 2014	Diarrhea, fatigue, endocrinopathy
Cetuximab	Periocular SCC	Anti-EGFR mAb	Off-label (head/neck)	Acneiform rash, infusion reaction
Rituximab	OAL	Anti-CD20 mAb	Approved (B-cell NHL)	Infusion reactions, neutropenia
Vemurafenib	CoM/UM	BRAF inhibitor (V600E)	Approved 2011	Photosensitivity, serous retinopathy
Dabrafenib + Trametinib	CoM	BRAF + MEK inhibition	Approved 2012/13	Pyrexia, less cutaneous SCC
Tebentafusp	mUM	ImmTAC bispecific (gp100/CD3)	Approved Jan 2022	CRS, rash, hypotension
Darovasertib	mUM	PKC isoform inhibitor	Orphan drug 2022	Hypotension, nausea, elevated ALT
Belzupacap Sarotalocan (AU-011)	Primary UM	VDC + photosensitizer	Phase III trial	Intraocular inflammation, raised IOP

BCC: basal cell carcinoma; SCC: squamous cell carcinoma; CoM: conjunctival melanoma; UM: uveal melanoma; mUM: metastatic UM; OAL: ocular adnexal lymphoma; CRS: cytokine release syndrome; IOP: intraocular pressure; ImmTAC: immune-mobilising monoclonal TCR against cancer; VDC: virus-like drug conjugate; CK: creatine kinase.

Many drugs are used outside their approved indications, and varying international regulations complicate standard treatment protocols.

Tebentafusp (Kimmtrak) is the first ImmTAC bispecific T-cell engager that binds gp100/HLA-A*02:01 with high affinity while activating CD3+ T-cells.9,18 In phase III trials (n=378), it yielded a 1-year OS of 73% versus 59% (HR 0.51; 95% CI 0.37–0.71; P<0.001) and median OS of 21.7 versus 16.0 months compared to investigator-choice treatments.[9] This survival benefit remained even in patients who progressed (15.3 vs. 6.5 months), indicating changes in the immune environment that standard imaging does not capture. [9,18] Low levels of ctDNA at week 9 predicted 100% versus 52% 1-year survival.[10] Cytokine release syndrome occurs in 86–90% of cases but is mostly mild. The first cycles require administration in specialized centers.[9,18] A major limitation is that tebentafusp is restricted to those with HLA-A*02:01, affecting about 50% of Caucasians versus only 6.5% of Asians. [9,18]

Darovasertib (IDE196), an oral PKC inhibitor, shows a 1-year OS of 57% as a single treatment for pretreated metastatic UM; when given with binimetinib, it reaches a 22% partial response with 79% tumour shrinkage.[11] The combination of darovasertib and crizotinib yielded a 31% partial response with complete tumour shrinkage.[11] Importantly, darovasertib targets GNAQ/GNA11 mutations and is not limited by HLA, making it applicable to about 90% of UM patients. [1,11]

Belzupacap sarotalocan (AU-011) is a virus-like drug that targets HSPG-overexpressing primary UM cells.[12] Data from phase 2 studies on suprachoroidal delivery indicated significant tumour growth rate reduction, 88.9% tumour control, and 88.9% preservation of vision, with only mild, short-lived intraocular side effects.[1,12]

Limitations and challenges

Major hurdles to implementation include:

- Cost and access: High drug prices hinder access, with tebentafusp costing about $22,512 per vial, vismodegib around $14,084 per month, and pembrolizumab about $5,861 per infusion, especially in low- and middle-income countries.[1,2]
- Off-label use: Many drugs are used outside their approved indications, and varying international regulations complicate standard treatment protocols.[1,2]
- Limited long-term data: The rarity of disease and short follow-up times in most studies limit long-term safety and effectiveness conclusions.[1,2]
- HLA restriction: Eligibility for tebentafusp in Asian and Pacific Islander populations is around 6.5%, significantly lower than the 50% in Caucasian populations, leading to health disparities.[9,18]
- Pediatric populations: Most approved drugs have insufficient safety and effectiveness data for children.[1,2]
- Resistance: Primary and acquired resistance to SHH inhibitors occurs in about 20%, and resistance to BRAF inhibitors can develop within a year; effective combination strategies need testing in future studies.[1,16]
- Response assessment: RECIST criteria may not accurately reflect true biological responses (pseudoprogression) to immunotherapy and tebentafusp, thus requiring new biomarker-driven assessment methods.[9,18]

More and more biosimilar forms of nivolumab are emerging on the market locally, which opens up some possibilities for broadening therapeutic options.

The Indian scenario

The most common types of cancer within the Indian ocular oncology spectrum include periocular and conjunctival melanomas, squamous cell carcinomas (SCC), and ocular adnexal lymphoma. With regard to melanoma, immunotherapy in conjunction with checkpoint inhibitors or anti BRAF therapy is currently becoming the main systemic approach in line with the global trend. Regarding SCC, platinum-based chemotherapy remains the main treatment regimen for this group of malignancies, largely due to economic limitations inherent to low and middle income countries (LMIC); although there is no question that checkpoint inhibitors such as pembrolizumab and cemiplimab would have been preferred, most of the patients lack access to these medicines owing to extremely high prices. The above problem becomes less and less pressing, however, as more and more biosimilar forms of nivolumab are emerging on the market locally, which opens up some possibilities for broadening therapeutic options. In regard to ocular adnexal lymphoma, intralesional and systemic rituximab are used based on the extent of the disease and its stage, following international guidelines.

There are several major obstacles hampering the application of new targeted therapies in India:

1. There are many medications approved by FDA and EMA that are not available in India.
2. High prices associated with these drugs render them unaffordable for many patients living in an LMIC environment.
3. Most off-label indications, representing a significant part of target therapy application in ocular oncology, are excluded from health insurance schemes as well as from any government-sponsored treatment program.

The overcoming of these systemic barriers through regulatory harmonization and pricing negotiation should make it possible to implement global advances in the field of targeted therapy for ocular oncology in India.

Conclusions

Targeted therapies have significantly changed how ocular cancers are managed. SHH inhibitors have greatly reduced the need for orbital exenteration in advanced BCC. Checkpoint inhibitors are improving outcomes in SCC and metastatic CoM. Rituximab has transformed OAL treatment at all stages. Tebentafusp represents the first documented survival benefit in metastatic uveal melanoma, while darovasertib and belzupacap sarotalocan address continuing unmet needs. Future efforts should focus on finding effective combination strategies to combat resistance, developing HLA-unrestricted T-cell engagers, obtaining long-term data on outcomes and quality of life, and ensuring fair access to these important therapies globally.

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Eye Spy

Don't ask me Y
Just find X.

A RELIC OF THE TWO REALMS
A ROGUE RIPPLE, THE MISS OF A BLINK
IT PREYS BENEATH THE SURFACE
SPY, SWIM OR SINK.

SHARAD ROHATGI
CROCODILE
NATIONAL CHAMBAL CROCODILE SANCTUARY
PALIGHAT, RAJASTHAN, INDIA

Solve for X

ANIRBAN DUTTA

1. **Email your answers to times@aios.org with your name, affiliation and phone number.**
2. **Book of choice for the first three who answer all 10 correctly!**
3. **Answers in the next issue.**

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is a Cornea Specialist practicing at his clinic, Chirag Eye Care in Prayagraj, Uttar Pradesh. After completing his MBBS from Medical College, Kolkata, he completed his DNB from Aravind Eye Hospital, Tirunelveli followed by a long-term fellowship in Cornea and Anterior Segment at L. V. Prasad Eye Institute, Bhubaneswar. He is also a Fellow of the Royal College of Surgeons, Glasgow [FRCS (Glasg) (Ophth)]. When he is not busy dealing with the slings and arrows of outrageous fortune in private practice, he prefers to spend his time reading arcane fiction and researching obscure trivia about random topics. Being an avid general quizzer in the fiercely competitive college quiz circuit of Kolkata in his MBBS days, he is a staunch believer in 'quizzing for quizzing's sake'.

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#1

The Code of X, created around 1750 BCE by the Babylonian king, is an early, 282-law legal code famous for *lex talionis,* or "an eye for an eye". It instituted proportional punishment, where if a man destroyed another's eye or tooth, his own was destroyed.

Identify X.

#2

X was a famous US President of the 19th century. He could not look a person straight in the eye because he had strabismus. Among the illnesses that X is either documented or speculated to have suffered from are depression, smallpox and malaria. It has been proposed that he could have had a rare genetic disorder such as Marfan syndrome or multiple endocrine neoplasia type 2B.

Identify X.

#3

In 1892 and 1900, X, travelled to India to visit Bhagvat Singh, the Thakur of Gondal, Gujarat- a former pupil at Edinburgh, who had become a personal friend. On his third visit in the winter of 1908–9, he died at Gondal on 3 January 1909. He was cremated on the banks of the River Gondli. In an unusual gesture for a Maharaja, and as a token of the esteem in which he held X, the Thakur *sahib* wore mourning robes and lit the

funeral pyre of his guru and friend.

X was a Scottish ophthalmologist who, among other things-described a key ocular finding in neurosyphilis-named after him.

Identify X.

#4

In 1905, X, a young Czech ophthalmologist, encountered a patient named Alois Glogar, a 45-year-old day farm labourer, whose corneas in both eyes had turned white-gray and opaque a year earlier while working with slaking lime. Around the same time he examined Glogar, an 11-year-old boy named Karl Brauer was brought to X's clinic with penetrating eye-injury to both eyes and iron metal foreign bodies irretrievably lodged in his eyes. When attempts to save Brauer's eyes were unsuccessful, X, with the boy's father's permission enucleated them and saved the corneas for transplantation into Glogar's. Although complications affected one eye, the other remained clear allowing Glogar to return to work. This was the first documented case of corneal transplantation.

Identify X.

#5

X, an Indian space-tech startup, has a name suggesting a connection with the "eye" and is developing satellites that combine optical imaging with Synthetic Aperture Radar (SAR) for all-weather Earth observation. Their flagship satellite, Drishti, is hailed as the world's first "OptoSAR" satellite, designed to operate through clouds and darkness.

Identify X.

#6

X is an American ophthalmologist and former tennis player who competed on the professional circuit in the 1970s and became widely known following male-to-female medical affirmation, when she fought to compete as a woman in the 1976 US Open.

The United States Tennis Association began requiring genetic screening for female players that year. X challenged that policy, and the New York Supreme Court ruled in her favor, a landmark case in transgender rights. Among the first professional athletes to transition, she became a spokesperson for transgender people in sports. After retiring from play, she coached Martina Navratilova to two Wimbledon titles.

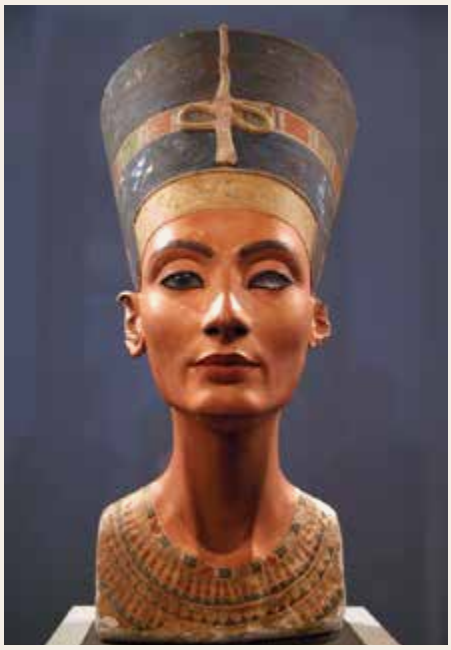
Identify X.

#7

One of the prized possessions of Germany's Neues Museum in Berlin is the bust (ca 1345 BC) of the legendary Queen X. She was the Great Royal Wife of the Egyptian Pharaoh Amenhotep IV and stepmother of the boy king Tutankhamun.

The bust is famous for having a missing left eye. Several theories abound for the same, with initial speculation that she lost the eye due to infection. These have been disproved, and the bust was likely a teaching aid.

Identify X.



#8

Author X lost sight in his right eye and sustained damage to his hand following a brutal stabbing attack on August 12, 2022 in New York. The attack left him with 15 wounds, including to his neck and chest. He described the daily struggle of this loss and detailed his recovery in his memoir *Knife*. X, an Indian born British national, has been threatened with death since 1989, with a fatwa being issued against him by the Ayatollah of Iran.

Identify X.

#9

X's eyes are highly specialized, allowing for independent movement horizontally, vertically, and a 360-degree field of vision. Their cone-shaped, scaly lids leave only a tiny pupil opening, acting like a camera lens for high magnification. They can zoom in on prey with binocular vision, enabling precise depth perception.

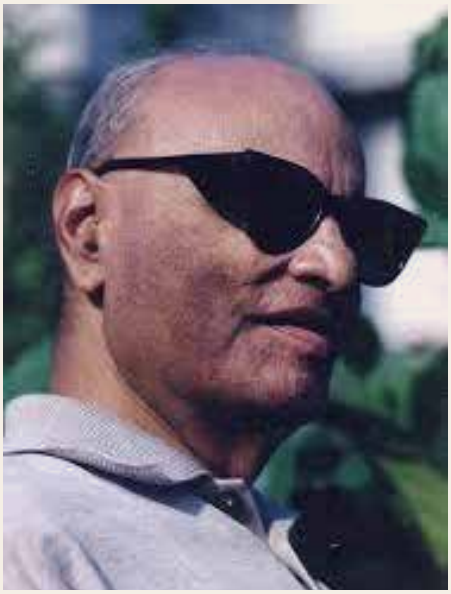
These specialized eyes are crucial for their survival, allowing them to remain camouflaged and motionless while still monitoring their entire environment.

Identify X, classified as a specialized lizard!

#10

Born in Dhaka on November 7, 1917, X lost his eyesight at the age of one-and-a-half due to smallpox. Despite this, he excelled academically. He was a pioneering Indian lawyer and politician who made history as the first visually impaired parliamentarian in independent India. A lifelong communist, he was a prominent advocate for the rights of the disabled. He was first elected to the Lok Sabha in a 1953 by-election from the Calcutta South-East constituency. He was re-elected in 1957 and served until 1962. He passed away in 2015.

Identify X.



Answers to Eye Spy January–March 2026 Issue

1. Alcon (Name is a portmanteau of the founders)
2. Bausch + Lomb (They ruled the camera lens market before focusing heavily on eye care)
3. Carl Zeiss
4. Rayner (They manufactured the first IOL for Ridley)
5. Allergan
6. The "Mission to Mars" Committee (NASA Advisory/Planning Boards)
7. Haag-Streit
8. Daigaku Eye Drops
9. Seiko or K. Hattori and Co. Ltd
10. SANS (Spaceflight Associated Neuro-ocular Syndrome)

Eyetalics

JUNGLE BOOK

TALES AND POEMS ON FORESTS, WILDLIFE AND THE BATTLE FOR SURVIVAL IN THE WILD

LET'S RUN AWAY
YOU AND ME
INTO THE WOODLANDS
WILD AND FREE.

Creative Corner.

MANISH NAGPAL
ASIATIC LION WITH CUB
GIR FOREST
GUJARAT, INDIA

The Jungle Stays With You

KAVERI BIRLA

Dr. Kaveri Birla
I am a third-year Ophthalmology Resident at Lady Harding Medical College in New Delhi, India. I am currently in that exciting phase of residency where you start discovering what truly drives you, and for me, that is oculoplasty. Oculoplasty draws me in for the precision and artistry it demands; it sits right at that beautiful intersection of function and aesthetics. Beyond the clinical side, I genuinely love connecting with people, colleagues, mentors, researchers, because I believe some of the best learning happens in conversation, not just in textbooks.

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The first mistake is to mistake the jungle for scenery. Scenery is obedient. Scenery is curated. It arranges itself for the eye, under the watchful eye of someone else. A garden declares its symmetry, and the idiosyncrasies of its gardener. The jungle does none of this. At sunrise, it offers no single view, no central subject, no easy place for the eye to rest.

The wild canopy is the first assault on order. Branches cross into branches, leaves gather in uneven patches, dead leaves pile up in the shadows, and the sky appears only in broken intervals, like some strange fractal made by wind and leaves. Some gaps are sharp, some are soft, some remain visible only for a second before the branches move again. Light enters through these openings in parts, falling on bark, dust, grass, stone, and the backs of leaves, so that the forest never becomes bright all at once. It awakes in fragments.

After a long stretch of trees and undergrowth, the watering hole appears almost suddenly, as a clearing where the forest seems to gather. The water is still at first glance, but everything around it is alert. Deer step towards it carefully, stopping often, lifting their heads, turning their ears in different directions before lowering their mouths to drink. Even in thirst, they do not fully surrender to the act of drinking. Their bodies remain ready to move. The slightest sound from the trees makes them pause, and for a moment the whole group seems to listen together, like an audience at the opera.

The birds move quickly between branches. Some call from hidden places, some sit high above the clearing and watch without coming down. A drongo gives a sharp call. A kingfisher flashes noisily through the shrubs on the riverbank. Smaller birds move in and out of the water, in search of breakfast. Their sounds fill the air in

broken pieces, each sound separate on its own, but create the most beautiful jungle symphony when heard together. The trees around the watering hole give the place its distinct, open shape. Some stand close to the water, their roots exposed and dark. Some lean slightly, as if the soil has shifted under them through centuries of weathering. Some have old scars, hollows, broken branches, creepers climbing over them, or nests hidden somewhere inside their leaves. They hold shade, perches, insects, birds, monkeys, and sometimes the marks of animals that have rubbed against their bark. In a jungle, a tree is not just a participant and functions quite literally the multistorey apartment we humans have fashioned out of concrete in our cities.

Then the deer's alarm call cuts through everything. It is sharp, repeated, and urgent. The animals at the water's edge lift their heads in a single synchronised movement. The birds grow unsettled. The park warden suddenly becomes alert as the driver slows our jeep. Nothing has appeared yet, but the mood has visibly changed. Something majestic is nearby. We look in the direction of the sound, but the forest gives no easy answer like the screens we so love to fidget with. Grass, shadow, dry leaves, branches, and sunlight all mix together, and every patch of undergrowth begins to look as if it might be hiding the fire-patterned beast.

The tiger is difficult to spot because it camouflages with the forest background. Its stripes break the outline of its body. The amber mixes with dry grass and fallen leaves. The black stripes disappear among branches and shadow. For a few seconds, one can look straight at the place where it is standing and still not fully see it. Then it moves slightly, perhaps the head turns or the shoulder shifts and its form clears up. What had looked like dead grass and lazy shade morphs into the majestic, awe-inspiring form of the tiger.

Unlike us, the deer have no need to see it to verify their worst fears. Their bodies are tense, their heads raised, their legs ready. The jungle at that moment is suddenly devoid of chaos. Even the creaking of a branch cuts through the silence. The tiger stands there without hurry, neither attacking nor retreating, as it basks in the attention of the jungle. And then, almost all at once the trumpets start blaring.

From the far side of the watering hole, beyond a screen of tall grass and low branches, comes the heavy, deliberate movement of the guardians of the jungle. Elephants! Their deep ringing trumpets, grass being pushed aside, leaves being pulled, a dead tree trunk cracking under their weight and then the shapes appear, one after another, not suddenly like the tiger, but with all the pomp of a festive procession. An elephant has no need to be stealthy. A matriarch steps forward with her calf close by her side, and behind her the herd follows through the old grassy paths that seem less like routes and more like memories worn into the land by hundreds of generations of the same enormous family.

The tiger, so complete in its authority a moment ago, has to humbly accept the change in the status quo. It does not vanish in panic, but it no longer feels it is the centre of attention. It slowly moves towards the water with a strange resignation, as if its thirst was all that drew it here. The elephant mother does not rush angrily; she does not need to. Her standing there is warning enough. She stands between the calf and the open water, her ears moving, her trunk testing the air, while the others spread around her and quench their thirst.

Immediately the tension begins to loosen. The deer lower their heads again and resume their grazing. The birds, after their brief panic, resume their calls from the branches. The kingfisher displays

its flashes of blue. The smaller birds begin their restless movement near the water. Even the tiger continues to drink as another thirsty creature among the thousands of creatures there. For a few seconds, the watering hole becomes the central theater in the universe as life assumes its most expansive character.

That is when the jungle becomes clearest, not because everything is finally visible, and all checkboxes have been ticked but because everything has found its place for a moment. The tiger has its stealth, the deer their alertness, the birds their warnings, the trees their patience and generosity, and the elephant, her quiet, immovable authority and the will of a mother. She is the loudest creature there, the most visible, the most feared and yet, the humblest amongst them. She is a heroine to the deer who only till a minute back were facing an existential crisis. With her calf beside her and the herd behind her, she brings scale, memory, and a kind of order that restores the chaos which fuels the jungle.

The jungle stays with you because it does not reveal itself in one clean view. It has to be watched slowly and continuously. It is not empty when nothing is visible, and it is not quiet when nothing is happening. It is full of small signals, hidden bodies, sudden warnings, and old routines continuing whether or not we are seeing or hearing them. Long after the jeep moves on, the jungle remains exactly itself, alive, alert, and complete, without needing to be seen by us.

The Beasts Within

RAHUL SINGH

Dr. Rahul Singh
I am an ophthalmologist and poet with a deep passion for both the art of healing and the craft of writing. Poetry, for me, is both refuge and revelation. My writing often draws from nature, mythology, and inner emotional landscapes, reflecting on survival, resilience, and meaning. Just as I strive to restore sight in my clinical practice, through poetry I seek to illuminate unseen truths and deeper perspectives. I believe both science and art share a common purpose—to help us see the world, and ourselves, more clearly.

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In the jungle of my ribcage, they roam,
untamed, unnamed, yet fiercely my own.

Anger comes first,
a lion with burning eyes,
prowling through my veins,
roaring at the slightest wound.
I face him bare-handed,
for if I run, he rules me.

Fear slithers behind,
a serpent of silent breath,
cold and patient,
coiling around my thoughts.
I tremble, yet stand still,
for panic feeds its poison.

Grief…
ah, grief is an elephant,
heavy, relentless,
crushing the earth beneath memory.

I do not fight her,
I walk beside her, slowly learning her weight.

Love is a wild horse,
beautiful, reckless, free,
it carries me to skies unseen,
yet throws me into dust without warning.
Still, I rise,
for I cannot live without its flight.

And hope,
a fragile bird in a storm,
wings trembling against the wind.
I cup it in my weary hands,
protecting it from the beasts,
even as they circle closer.

This is my wilderness,
no map, no mercy, no escape.
Yet I fight, I fall, I rise again.
For to survive them
is to become something stronger than them all.

She Belongs to None

DEBALINA GHANTA

Dr. Debalina Ghanta
I am working as an Associate Consultant in the Department of Glaucoma Services in Sankara Nethralaya, Kolkata. I have completed MS Ophthalmology from NRS Medical College and Clinical Glaucoma Fellowship from Sankara Nethralaya, Chennai, with FAICO degree in Glaucoma, conferred by AIOS. Beyond my profession, I like to immerse myself, while sipping caffeine, in healing, slice-of-life fictions.

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There lives a forest sprite
Dancing through the valley of flowers,
Deep in the woods, far from the clamour of human world
Fluttering wings shimmered in rainbow colours.

Waist-length hair touched by golden sunlight,
She loves the soft carpet of grass beneath her feet.
Protected by the canopy of tall trees in summer,
She hums the chorus of the gurgling monsoon river.
Laughing with the jubilant roar of the waterfall,
Sniffs the redolence of the earthy scent of first rainfall.
Giggling to autumn cloud's hide-and-seek,
Murmurs the birdsong on a chilly breeze.
Running through winter's silver-white fields,
She lies down to stare at the dew-pearls on the grass.
Draped in a veil of mist
Dances through the spring's colorful carpet of leaves.

The branches swirling with the wind,
bearing the weight of sky and clouds afar,
Singing lullaby of decade old stories,
only a true heart can hear.

There lives a forest sprite
Her heartbeats bear echoes of time in moonlit night.
She is free in her wilderness, she belongs to none
Untamed by the world, answered by the star and sun.

She is the forest, the forest is she.

The Jungle of Stereopsis: *A Girl-cub's Guide Through the Squint Clinic*

DIVYA CACULO

Dr. Divya Caculo
I am a Pediatric Ophthalmologist and Strabismologist currently practicing at Sankara Eye Hospital, Bangalore. Originally from Goa, I earned my MBBS from Goa Medical College, followed by specialized training at KIMS Hubli and GMC Surat, eventually completing my fellowship at Sankara Eye Hospital. Beyond the clinic, I am a Black Belt in taekwondo and deeply passionate about the arts. My musical journey spans from being a band vocalist to training in Hindustani classical music and Bharatnatyam. I strive to bring the same precision and rhythm found in my hobbies to my medical practice.

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In the jungle of residency, the Squint clinic, Council Rock, is a much-avoided place of profound alienation. Here, the struggle isn't against a murky cataract or a clouded cornea; it is a battle against the 'Red Flower' - hidden forces of alignment.

To a Girl-cub, squint is like a wild Red Flower that refuses to back down. Taming this Red Flower and the ribbons which are hidden beneath the white sands of the Tenons is what the Girl-cub should learn. The Girl-cub hides behind Bagheera as she sees him skilfully mastering and controlling the leashes of muscles like red ribbons, with grace.

"If one is too tight, the gaze gets fixed; if one is too slack, the gaze wanders into the peripheral shadows," he says as the Girl-cub looks in awe. He hands the Girl-cub a muscle hook, a curved silver claw that feels heavy and foreign in her hand. *"You have watched me hunt. Now, you must find the 'beast' yourself."*

The Girl-cub's fingers tremble as she approaches the thin, translucent veil of the conjunctiva, and clears the vines of the Tenon's capsule where the ribbon lay hidden like a tiger in the tall grass.

"Softly," Bagheera says, leaning over her shoulder. She feels the strength of his presence, a shield against the chaos of the clinic. *"Do not fight the forest. Slide the hook under the belly of the muscle."*

With utmost care, the Girl-cub proceeds and feels the hook catch. A firm, red ribbon of flesh rises from the depths, isolated and captive. It was her first "kill." The muscle against the steel—a trapped, wild thing.

"Good," he whispers, *"Now, remember: the knot you tie today determines whether the path becomes clear or wanders forever in the shadows."* It can be a frustrating trek for the Girl-cub, for sometimes, you tighten a knot only to find the eye has drifted in a new, unforeseen direction, as if the jungle itself is shifting the path beneath your feet.

In the clinic jungle, the Girl-cub slowly learns the language of "tropias" and "phorias". She spends her days with glass triangles- learning a lesson in binocular diplomacy, trying to coax two separate, warring images to merge into one peaceful clearing.

The reward is a unique kind of peace and unison. It's the moment the wild ribbons, once darting, finally lock together and the world snaps into three dimensions.

Bagheera says to her, *"To be a Master of the Squint, you must have the heart of a hunter and the touch of a weaver."*

Now, she is no longer a shivering Girl-cub. She stands at the Council Rock, looking at the two aligned ribbons, realising that while she may leave the jungle, the rhythm of the six ribbons will always beat in her heart.

Tell Me Why

AJAY I. DUDANI

Dr. Ajay I. Dudani
I am a Professor of Ophthalmology and a Senior Vitreoretinal Surgeon at Mumbai Retina Centre. My passion is music, tennis and retina and I am an avid reader. The aim of my life is to know myself through advita and zen.

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Forests, jungles, wildlife—
that was the title given,
as if the danger lived in leaves,
as if the threat was hidden.

We say life is hard
in forests of the earth,
yet harder still in concrete jungles
where greed decides our worth.

Animals are faithful things,
they can be fierce, yet tame;
they do not burn their children's homes
or kill in glory's name.

But genocide stains human hands,
a slap upon our face;

the apocalyptic human race
runs mad against its grace.

Lebanon, Iran, Gaza Ukraine
Israel, USA same refrain
them versus us, old, poisoned words
that generations hear.

Artemis circled Moon and Earth,
looked back and saw us blue;
a beautiful and fragile sphere,
still whole from that far view.

Yet we are bombing our own home,
blasting roof and stone,
which animals do not conspire
to do against their own.

So, who is wild and who is tame?
We are to blame for this game.
Destruction of civilians below,
missiles in the skies aflame.

Drones we send to distant hands,
killings called a ploy;
while beasts of field and beasts of sea
don't murder out of joy.

Jungles are a joy to breathe,
our cities choke in haze;
the world divided like never before,
set burning by the few who graze.

Wild creatures in the jungle
never kill their kin to win;
while children are extinguished here,
and poison clouds grow thin.

Trees massacred, environment stained,
man, heal thyself at last.
Save our Mother Earth, I pray,
from the wild animals of our class.

The battle for survival now
is not in fang or claw,
it lives within the human heart,
its violence and flaw.

There are no others left to blame.
No beast to drag or chain.
Unless we tame the wild in us,
we all die just the same.

Lanterns of the Whispering Woods

IMON ROY

Dr. Imon Roy
I am a second year postgraduate resident in the Department of Ophthalmology at Silchar Medical College and Hospital, Assam. My primary interests lie in vitreo-retina, clinical research, and academic writing. I have actively engaged in conference presentations and publication-oriented works, particularly in awareness-based and clinical studies. Alongside medicine, I am deeply inclined toward creative writing, especially poetry inspired by nature and human emotions. I aim to blend scientific precision with empathetic care while continuing to explore meaningful intersections between medicine and the humanities.

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In the quiet, dwindling twilights aquiver,
When the sky forgets its last shade of gold,
Elysian specks arrive like whispers;
The darkness has learnt to hold!

Lanterns stitched beneath the ribs, promises that glow,
Memories returning in fragments, hesitantly flickering slow.
Like hope learning to speak again after a long season of silence;
In brief sentences of light, each pulse breathing in jubilance.

Drifting through the canopies to mists like lost constellations,
Not crowned by the sun, nor announced by the moon,
Soft rebellions engraved in fragile bodies,
Burning without fear of losing soon!

And for a moment, the world forgets its heaviness,
The night listens to their songs of dreams;
The ancient woods awaken from a deep slumber,
Stars of resilience, defiance in million beams!

Because even the smallest spark,
Can make the dark feel like it's listening,
That darkness is not defeated by brilliance but by persistence;
By the soft, stubborn insistence of shining anyway!

The Last Light from the Jungle Road

PRATIK PRABHAKAR

Dr. Pratik Prabhakar
I am a first-year postgraduate resident in Ophthalmology at Darbhanga Medical College and Hospital. I began writing poetry in childhood, and my work has since appeared in newspapers and magazines. Alongside medicine, I continue to write, believing that good patient care requires empathy, listening, and an understanding of each person's story.

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The call came at 6:00 p.m., just as the evening OPD was closing.

"Corneal retrieval. Consent taken. Village-Bhitha, on the forest side," the coordinator said.

Sister Meera glanced at the clock. *"Time of death?"*

"About an hour ago."

She nodded. *"We should leave now."*

The team was small, standard for outreach. Dr. Vinay, Senior Resident; Dr. Abhishek, a first-year junior resident; Meera, the assigned nurse; Shambhu, the driver; and Raghu, a Home Guard to guide them.

They checked the cornea retrieval kit: sterile trephines, Cornisol medium, povidone-iodine, gloves, speculum, scissors. Everything had to be intact. There would be no second chance.

By the time they left town, the sky had turned heavy. May humidity hung thick, and the smell of wet earth rose even before the rain began.

"Road will be bad after the canal," Shambhu said.

Rain started—first a drizzle, then a sheet. The wipers struggled. Visibility dropped to near zero. The tar road ended, replaced by a *kuccha* track leading into the forest.

Meera held the box on her lap. *"Sir… how long do we have?"*

"Best within six hours," Dr. Vinay replied. *"We're still okay."*

Lightning flashed, revealing deep ruts filled with water.

The jeep dipped hard.

"Arre—" Shambhu corrected the steering, but the rear wheel spun in the mud.

He tried again. The engine growled, tyres kept slipping.

"We're stuck."

Rain drummed on the roof. The engine was still on, but the jeep wouldn't move.

Raghu opened the door slightly, then shut it quickly. *"Slush up to the axle. Forest starts here."*

Dr. Vinay checked his watch. 7:25 pm.

"Options?"

"Village is 2–3 km inside the forest," Raghu said. *"Walking in this rain…is not safe a safe option."*

A distant sound came - sharp, brief.

Dr. Abhishek stiffened. *"What was that?"*

"Tiger, maybe. Sometimes leopards prowl too."

Not dramatic, but not ignorable.

"We stay in the vehicle," Dr. Vinay said. *"Let's conserve battery."*

Headlights were turned off; only a dim cabin light remained.

The rain intensified. Water began seeping through the doors.

Shambhu tried rocking the vehicle, but the tyres dug deeper.

"Don't burn the clutch," Dr. Vinay said.

Time slowed.

The network flickered—then vanished.

Raghu stepped out briefly and returned. *"No houses nearby."*

Outside, faint rustling could be heard punctuated by occasional howls—nothing clear, but enough to scare.

"Sir… what if we can't reach?" Dr. Abhishek asked quietly.

Meera answered, *"Then we inform and stand down. But we try till it's unsafe."*

They kept it practical. Windows closed. Doors locked. The horn sounded occasionally. Conversation stayed low.

Around 9:00 pm, the rain eased.

"Let's try again," Shambhu said.

They stepped out into ankle-deep mud, placing stones and branches under the tyres.

"Push when I accelerate."

"One, two..."

The tyres spun.

Again.

On the third attempt, the jeep lurched forward.

"Keep going!"

Another push.

The wheel caught traction.

The jeep climbed out.

They got back in—wet, breathing hard, but moving.

"Slowly now," Meera said.

They reached the village near 10:00 p.m. A small group waited with a lantern.

Inside, the body lay respectfully prepared. Consent papers were rechecked. Sterility was maintained as best as possible.

Dr. Vinay, assisted by Dr. Abhishek, performed the enucleation steadily. Meera assisted with precision, despite the fatigue.

The work was completed. The eyes were preserved.

As they packed up, a young boy stepped forward. He had been silently watching.

"Doctor saab… will he be able to see now?"

Dr. Abhishek paused.

Dr. Vinay answered gently, *"No. But someone else will."*

The boy nodded, as if that was enough.

The return journey was quiet. The storm had passed.

Dr. Abhishek looked out and said, *"It didn't feel heroic."*

Dr. Vinay replied, "It isn't. It's just doing the job properly."

And that night, somewhere, two corneas began their journey toward restoring sight—because a team chose patience over panic, and method over fear… and because a child understood, without explanation, what it meant to give sight beyond life.

Whispers Beneath the Canopy

GAURAV PANDE

Dr. Gaurav Pande
I am Cornea Refractive Fellow at Narayana Nethralaya. I have presented multiple papers and posters at national and international conferences. I am also a passionate admirer of poetry and literary arts and actively seek out literary events, open mics, and discussions that celebrate creativity and diverse voices.

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In the heart of the jungle, where whispers reside,
Beneath the thick canopy, wild secrets hide.
The call of the tiger, fierce, regal, and bold,
A symphony of life, in stories untold.

From emerald leaves, where the sunlight creeps through,
The dance of the monkeys, in skies ever blue,
A tale of survival where instincts prevail,
In the wild, every heartbeat tells tales that unveil.

The rustle of branches, a warning sign clear,
As creatures, both timid and mighty, draw near.
The antelope leaps, with grace it does glide,
While shadows of predators patiently bide.

The river winds gently, a silver-threaded line,
Where otters and crocodiles both intertwine.
Each ripple, a newstory, and each splash, a new song,
In these battlegrounds of nature, both fragile and strong.

Beneath the vast stars, where the moonlight gleams,
The jungle breathes life, igniting our dreams.
With every heartbeat and whisper of fray,
We learn from the wild, come what may, come what may.

So, heed the soft lures of this mystical land,
Where every step forward is written by hand.
For in the embrace of the green, wild and vast,
The spirit of survival is never unsurpassed.

Roots Shaken by Distant Thunder

R. PREETHIGHA

Dr. R. Preethigha
I am currently practising in Comprehensive Ophthalmology Department at Anand Eye Hospital, Madurai, Tamil Nadu. I pursued my MBBS degree from Government Mohan Kumara Mangalam Medical College, Salem and MS Ophthalmology from Government Coimbatore Medical College, Tamil Nadu. I am a passionate reader, a budding writer and a creative calligrapher. Some of my favourite authors are J.K Rowling, Cecelia Ahern, Jojo Moyes, Beth 'O Leary, Meg Shaffer and David Bech. Amidst the hustle bustle of clinical and mundane life, I find my solace in fiction and non-fiction books, poetry and calligraphy.

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Timeless land enthroned in emerald canopy,
Up above where flocks sing in the wind,
Under tangled branches herds and pack graze in verdant terrain,
Bounded by rustic giants and blue of tranquillity.

Warm-blooded dwellers wander in vast woods,
Alongside wings of feathers whistling in the heights,
Colony of soft paws, roll and play under the honeysuckle leaf,
A thousand uneven lives breathe in leaves and shadows,
Where harmony is built from difference.

In a heartbeat, might green hushed,
Streaks of pinions slide through mobbing,
Where breeze break into freeze,
Just then, an obnoxious ingress creep.

Shades of deliberateness slither under the realm,
Whorls of foliage fumble beneath the rooted dark,
Mismatched breaths cease in mid-shift,
A presence, settled that did not belong.

Soft paws, feathered arcs and coats of fur burst into fright,
Through hit or miss motion of plight
Small hands slipped through blind sight,
Only race and rush remain in skylight.

Some survived space beyond the day
Some vanished down the train,
A small step stumble behind,
The thicket suspended without a say.

The broken realm remit into silence,
All is dream within a dream
Some spaces no longer moved,
An ogre force gone in the wind.

Not all hunts were claws and teeth
Some arrive without a sound,
The rhythm of living breaks apart,
The world holds forests of its own.

The Mirror of the Wild

UMA SHROFF

Dr. Uma Shroff
I am a Pediatric Ophthalmologist and Strabismus Specialist at Tejas Eye Hospital, Mandvi, Gujarat. I completed my MS in Ophthalmology from B.J. Medical College, Ahmedabad, followed by a fellowship at Tejas Eye Hospital, and observerships at Moorfields Eye Hospital, London, and Aravind Eye Hospital, Madurai. I was invited to Japan under the Sakura Science Program, visiting Kitasato University and the University of Electro-Communications. Actively engaged in research and teaching, I am passionate about mentoring, singing, and writing, and believe in balancing professional excellence with family, creativity, and mindfulness.

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We build walls of glass and concrete to convince ourselves we have outgrown the wild. Have we? Really? We see the mother lion leaving a limping cub behind, or the elephant herd walking steadily away from a fallen, thirsty calf about to die, and we call it cruel. But cruelty comes from intent, from wanting to hurt. It is selfishness in its purest form. What happens in the wild is born of necessity. If the mother stops, she may lose all her cubs. If the herd waits, they may all die of thirst. They do not have any choice. It is the brutal law of survival. Unlike humans, where all greed, all selfishness that come into play. When the mother leopard hides her cub in the treetop, she knows there is no perfect safety. There is only the lesser of the two dangers. She leaves her cub with the heaviest heart to go search for food and makes it back as soon as possible.

In our world, we tend to complicate love. We tie it to our egos, keeping a quiet score of what we get in return. We hope for a "thank you" or obsess over the legacy we will leave behind. We view children as an insurance policy- *"bacche to chahiye, hamara budhape ka sahara banege"*; or a vessel for vanity- "*beta to chahiye, hamara khandan aage badhayega."* Nature, however, strips love down to something raw and absolute. Consider the Giant Pacific Octopus. For months, she refuses to eat, protecting her eggs as her own body slowly consumes itself to fuel her devotion. The moment her babies drift into the current, she dies. Her entire existence builds to that single, quiet act of surrender, giving everything she is so that something else can be.

On the frozen plains of Antarctica, the Emperor Penguin father balances a newborn chick on his feet, tucked beneath a warm fold of skin. He must be precise; if the chick touches the ice for even a moment, it is gone. To survive the wind, thousands of these fathers huddle together, moving as a single organism. Those on the freezing outer edges eventually waddle into the warm center,

while those who have warmed up rotate back to the front. That is what survival in the most brutal of the environments looks like.

We spend our lives trying to mitigate risk, constructing a world where we never have to fall. But the wild demands surrender. The Barnacle Goose chick must step off the steep rocky cliffs before it even possesses wings to fly. Only few will survive. The parents are faced with the most brutal part of their lives, to painfully wait and watch to see how many survive.

Yet, the wild is not devoid of connection. It simply shows us that connection serves a purpose greater than the self. The beehive moves as a single breathing entity with one motto, to protect the queen and offsprings; proving survival often requires the dissolution of the individual. The Sarus Cranes, commit for life, if one partner is lost, the other one dies too.

We stare into the wild and feel unsettled because it holds up a mirror to our deepest anxieties. It strips away our comforting illusions. It does not pretend that life is fair, and it does not promise that good intentions will be rewarded. It reminds us that underneath our modern anxieties, we are still bound by the same ancient rhythm: to survive, to protect, and to continue. We are not separate from nature; we are simply (un)aware of it. Survival is not a promise; it is earned. And so is every moment of life that we are lucky enough to witness.

The Silent Jungle

SHAFFI CHOPRA

Dr. Shaffi Chopra
I am a Phaco-refractive Fellow at Centre for Sight, Delhi. My journey in ophthalmology has been shaped by a deep fascination for precision, optics, and the delicate balance between science and art in surgery. Beyond clinical practice, I enjoy expressing medical experiences through writing, transforming moments from the operating room into reflections on life, discipline, and human resilience.

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The jungle is never silent.
It only appears so to those who do not know where to listen.

I learned this not in the wild, but under the glaring white light of an operating room. Where silence is discipline, and every movement carries consequence. Where the faintest tremor can turn victory into regret.

In the jungle, survival belongs not to the strongest, but to the most aware. A predator listens before it leaps. A prey senses before it flees. Every life is balanced on instinct sharpened by experience.

Much like us.

There are days when the case looks simple—routine, predictable. And yet, like a forest that hides danger beneath still leaves, complications wait in silence. A slight bleed. A sudden shift. A moment where time slows, and every decision echoes louder than words.

In that moment, you are alone.

No applause. No reassurance. Just you, your training, and the quiet pulse of responsibility.

The jungle does not forgive hesitation.

And neither does the human body.

But survival is not just about precision. It is about respect—for the terrain, for the unknown, for the life that trusts you blindly.

Over time, you learn to read the silence. To sense when something is about to go wrong before it does. To act not out of panic, but from a calm that comes only after walking through storms.

That is when you realize,
You are no longer afraid of the jungle.

You have become a part of it.

The Jungle Calls

SHILPA DAS

Dr. Shilpa Das
I am a cornea specialist working at Narayana Nethralaya, Bangalore. Apart from clinical ophthalmology practice, I like to write poems, essays and give lectures. Poetry is a form of expression to me and it comes as a natural flow when I experience a particular moment. It is a world apart; nothing but reality seen through a filter of beautiful colors.

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Close your eyes and listen
To the beats missed often
That of the beast, that of the priest
That of the ever-blooming yeast.

The jungle wakes up with the sun
Flora, fauna, everyone
No creature too small, no creature too tall
The dense forest is a haven to all.

The fast predator, an even faster prey
The mighty ones that travel by the day
A beautiful but delicate ecosystem
Exists, syncing with nature's way.

The woods, with beauty that's endless
Leaves one in awe, leaves one speechless
It opens the eye to mother earth's charm
Do preserve it with all might and do no harm.

Homeless Under Heaven!

JUI GHAREKHAN

Dr. Jui Gharekhan
I am working as an Associate Consultant at Centre For Sight, C.G.Road, Ahmedabad. I am phacoemulsification surgeon. I completed my MBBS from Saurashtra University with Gold Medal and postgraduation from M and J Eye Hospital. I have worked in Bangalore for three years at Shekar Eye Hospital, Vasan Eye Care and Apollo Hospital. After returning to Gujarat, I worked at Santram Eye Hospital and Dr. N.D. Desai Medical College and Nadiad Civil Hospital.

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Yesterday I slept beneath the shade,
Today no roof, no home is made.
My roots are torn from earth's embrace
Where do I hide my hatchlings safe?
They used to jump without a care,
But now they tremble, gripped by fear.
"Mother, where will you take me, dear?"
Their little voices, sharp and clear.
Forever running for our lives,
From tigers' roars and crocodiles.
Yet still we love the breezes cool,
The waterfalls, our wildlife's jewels.
We chase the butterflies in flight,
And giggle under morning light.
How beautiful this world, this sky,
Why can't we humans see, oh why?
God is an artist, skilled and grand,
Who carved this earth with loving hand.
For nature gives and gives for free,
Asks nothing back from you or me.
My life may be both short and wild,
Uncertain as a forest child.
But I will live it full and brave,
With fear left buried in its grave.

Rings of Time

LAKSHMI KUNIYAL

Dr. Lakshmi Kuniyal
I am an ophthalmologist with over 15 years of clinical experience in comprehensive ophthalmology, and specialization in retina. I received my advanced training from the prestigious Sankara Nethralaya, Chennai. I am actively involved in postgraduate teaching and regularly participate in academic conferences through presentations and discussions. Alongside my clinical and academic work, I have a keen interest in creative writing and contribute articles to creative forums and professional websites, reflecting my passion for both medicine and thoughtful expression.

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In the middle stretch of life
when the road behind grows long
and the road ahead begins to narrow,
I walk among the trees.

The forest knows this age well.
It has seen the sharp summers of youth
and the slow winters of patience.
Its branches carry both scars and shade.

Some trees lean where storms once pushed them,
some stand tall where lightning once struck.
Yet none have abandoned the sky.
They rise again, leaf by leaf.

I see myself in their quiet endurance—
roots gripping unseen depths,
trunks weathered by seasons,
still reaching upward without complaint.

Life too has its monsoons.
Winds of loss bend the spirit,
dry seasons test the strength of hope,
and sudden storms shake our certainty.

But the forest teaches gently.
A fallen leaf feeds tomorrow's soil.
A broken branch makes room for light.
Even decay prepares the ground for growth.

So in this middle age of living
I learn what the forest has always known—
that strength is not in never bending,
but in rising after every wind.

And like these patient trees,
I gather the lessons of years
into quiet rings of wisdom,
standing a little steadier each season.

For both the forest and the human heart
grow not in perfect calm,
but through storms endured,
until we too learn
to stand tall beneath an open sky.

Into the Wild

NAVYA NAVEEN KALRA

Dr. Navya Naveen Kalra
I am a second year Ophthalmology Resident at GMCH, Chandigarh. My love for ophthalmology stems not just from the beauty of the world that eyes perceive but also from the depths that they reflect. I enjoy expressing myself through art and strive to grow as a person holistically. I believe that I have a lot to learn from the world around me and I yearn to be better everyday.

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The jungle is a hunting ground,
A hierarchy of sorts,
The fittest survive here,
With no mercy for the ones who fall short.

Just like the field of medicine,
There's only one way in.
You might try to escape,
But the doctor in you will always win.

There are early sunrises and beautiful sunsets,
The morning hustle and bustle, the constant fear of death.
And amongst all the chaos, even new life blooms,
In the arms of occasional symbiosis, a small smile looms.

Many dare to enter the jungle every year
Lots have survived its decades of adventures
A few have failed and skewed
But even though the jungle is a dynamic nest
Its existence is a timeless paradigm.

Cross-eyed

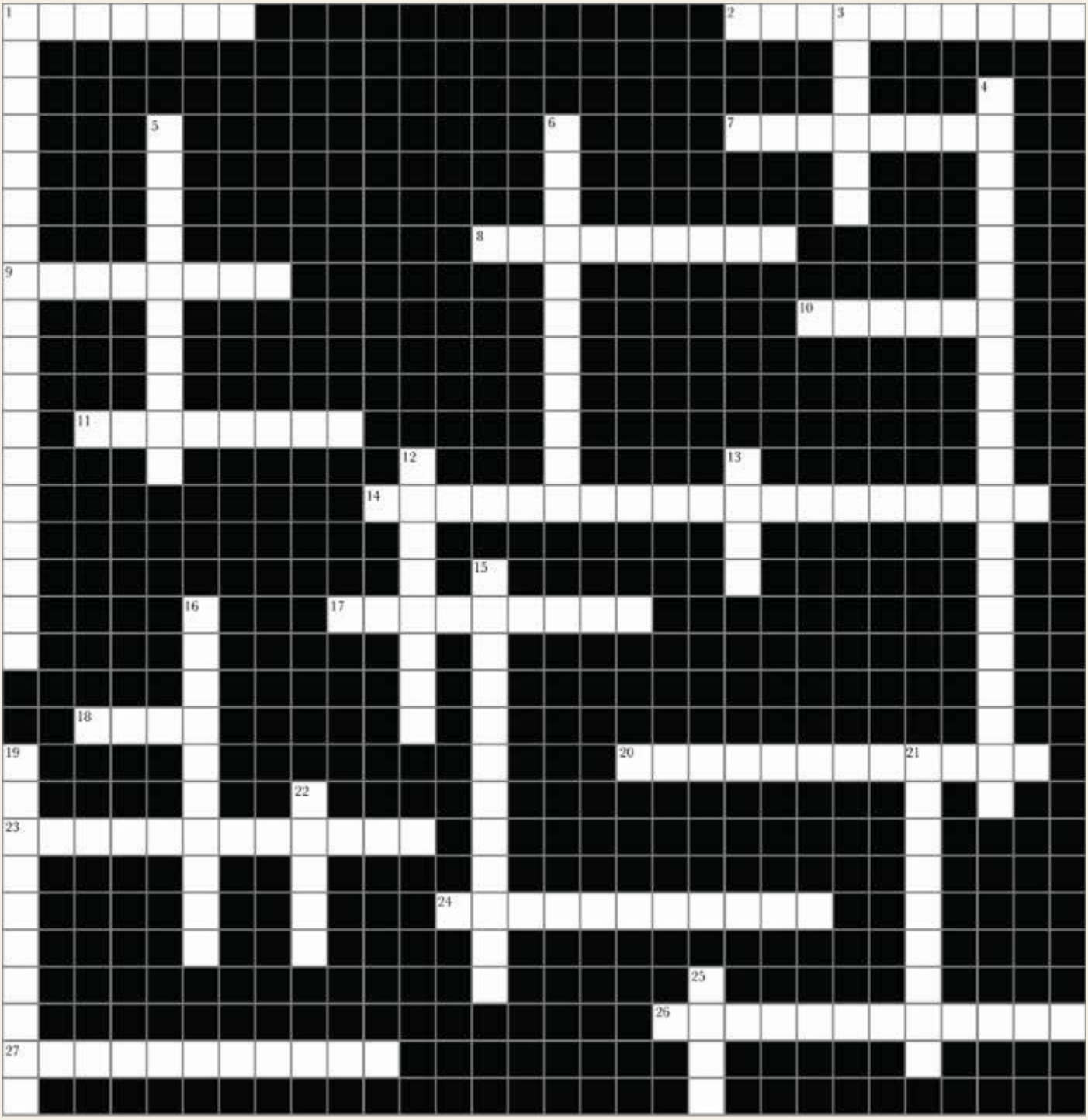
FLICK THE WIND
AND SKIM THE RIVER,
FIGHT IN FLIGHT
HUNT FOR A PUZZLE IN BLACK AND WHITE.

Ophthalmic crossword.

KEERTHI TEJA THIRUKOVELA

THE LITTLE EGRET
GODAVARI RIVER, PAPIKONDA NATIONAL PARK
ANDHRA PRADESH, INDIA

1. Take a print out. Click here for the Crossword file here.
2. Solve the crossword.
3. Take a picture and email to times@aios.org with your name, affiliation and phone number.
4. Solution in the next issue.
5. First three winners get a book of their choice.



Across.

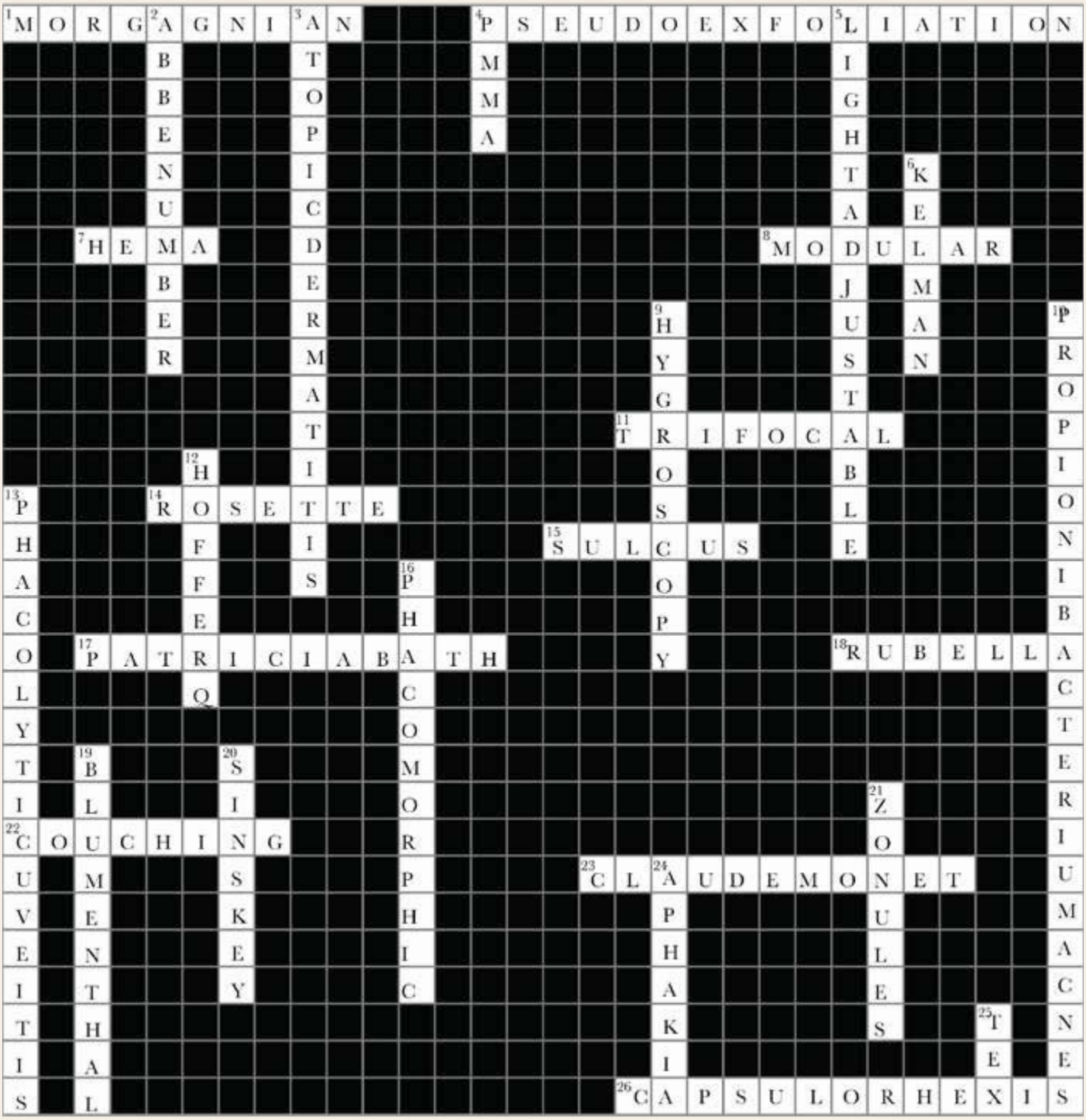
1. The first mortal woman created out of earth by Hephaestus, bestowed by all Gods with their choicest gifts, thereby, naming her 'the all endowed.'
2. Rare B-cell non-Hodgkin lymphoma with an aggressive clinical course characterized by a translocation (11,14).
7. First lymph node to receive drainage from a tumour.
8. Benign mass of disorganized tissue in their normal location.
9. Intraepithelial spread of malignant cells separate from the main tumour.
10. 4th sign of Zodiac.
11. New growth?
14. Pulitzer Prize winning Indian-born American haemotologist, oncologist and author.
17. Radioisotope with a half-life of approximately 1 year used for ophththalmic brachytherapy.
18. The cancer genome atlas.
20. He is credited with the development of chemo-thermotherapy for retinoblastoma treatment, and is recognised for his role in cloning of the RB1 gene and determining the location of RB1 gene on chromosome 13q14.
23. Benign multi-cystic, no flow type vascular orbital tumour.
24. Textiloma
26. Basal cell nevus syndrome.
27. Benign retinal tumour associated with tuberous sclerosis.

Down.

1. Most common benign epithelial tumour of the lacrimal gland.
3. Malignant peripheral nerve sheath tumour with rhabdomyomatous differentiation, named after a newt.
4. Retinoblastoma rosettes.
5. German botanist and dermatologist with eponymous multinucleated cells that he called "xanthelasmatic giant cells."
6. Benign choroidal vascular tumour with high internal reflectivity on ultrasound.
12. FDA approved immunotherapy for adult patients with HLA-A*02:01 positive metastatic uveal melanoma.
13. Conjunctival melanocytic intraepithelial neoplasia.
15. Zimmerman's benign pigmented lesion of the optic disk that had previously been erroneously considered malignant; aka hyperpigmented magnocellular nevus of the optic disk.
16. Most common intraocular malignancy of in adults, most commonly affecting the choroid.
19. First and only oral medicine FDA-approved for adults with VHL disease-related tumors.
21. Founding member of the Rochester Civic Theater, he played Elwood P. Dowd in "Harvey," in the first 5 years of production, and was also the author of the textbook 'Orbital Tumours.'
22. _____-1 mutation associated with medulloepithelioma.
25. CD34 positive benign mesenchymal tumour of the conjunctiva.

Solution for January–March 2026 Issue.

Crossword



Winners!

Cross-eyed January–March 2026 Issue

Dr. Vinaya Mallya

is working as an Assistant Professor at Kanachur Institute of Medical Sciences, Mangalore. She completed her postgraduation at the prestigious RIOGOH, Chennai under renowned mentors. She is a keen academician with a deep passion for teaching and quizzing. She also enjoys cooking and considers it a way to connect with her loved ones. She is a dutiful mother to a bubbly toddler and finds creative ways to spend time with him. Always surrounded by books, she hopes to publish her own book someday.

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Dr. Vijay Kumar Gupta

graduated from Guru Nanak Eye Centre, Maulana Azad Medical College, Delhi in 1985. He joined a Government job and practiced general ophthalmology with an inclination towards oculoplastic surgery. He was awarded the The Delhi State Award for Meritorious Service for the year 2011-12. He retired from job in 2023 from Sanjay Gandhi Memorial Hospital, Delhi.

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Dr. Saranya Santhosh

completed her MBBS from Kanyakumari Government Medical College and DNB from Sankara Eye Hospital, Pammal. She finished her Cornea and Ocular Surface Fellowship at Darshan Eye Care, Chennai under the mentorship of Dr. Srinivas K. Rao. She is currently working as Cornea Consultant at Sankara Eye Hospital, Pammal, Chennai. Her keen interest is in lamellar keratoplasty and loves to solve puzzles.

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Roll of Honour

Dr. Vasavi Karuparthi

Dr. Anita Kumari

Dr. Arun S.

Dr. Suraj Bajwa

Dr. R. S. Bajwa

Dr. Jeel Hingu

Winners!

Eye Spy January–March 2026 Issue

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Roll of Honour

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Dr. Vinaya Mallya

Dr. G. Rathna

Dr. Adwitiya Sarkar

We would love to receive feedback from you!

If you have a suggestion,
Or a simple line of appreciation.
Even words of criticism,
Commentaries and contributions...
Write to us on times@aios.org

ADWITIYA SARKAR
OSPREY
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And into the forest I go, to lose my mind and find my soul - John Muir