CENTRE *for* PERSONALISED MEDICINE

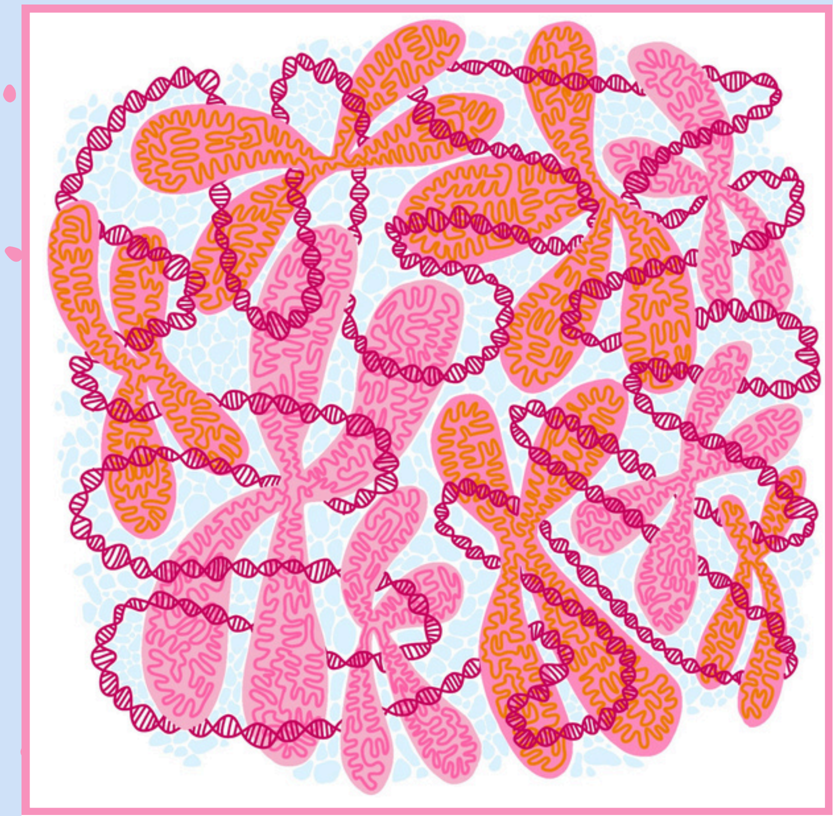
PRINT EDITION

The Gene'Zine

OXFORD PERSONALISED MEDICINE SOCIETY

ISSUE 8

Genes Unboxed



HT-TT
2025

DISCLAIMER: ALL GENES EXPRESSED
ARE OUR OWN

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We extend our heartfelt gratitude to Izzi Reid for her illustrations for our cover page and section headers

HT-TT '25

WELCOME FROM THE EDITORS-IN-CHIEF

GEETIKA KUMAR

Hi, I'm Geetika, a 5th year medic at Corpus Christi College. I am so excited for you to read the HT-TT25 issue of the Gene 'Zine - this is my final issue as co-editor-in-chief, and I have really enjoyed my time working on the magazine to bring the personalised medicine world to you, our readers.

This issue has articles covering a wide area of topics, including some of my favourite areas of personalised medicine such as the microbiome, immune-mediated diseases and immunotherapies, and ethical dilemmas posed by novel techniques and AI.

We are incredibly grateful to our writers, editors and illustrators for all the hard work they have put in to make this issue possible. I hope you enjoy reading it as much as we've enjoyed putting it together!

JOSHUA LAM

Hi! I am Joshua, a second year biomedic studying at Teddy Hall. Being part of the Gene 'Zine is such a cool way to explore personalised medicine. I am interested in the application of precision medicine in age-related problems. In particular, it provides me a platform to explore personalised medicine beyond novel therapeutics.

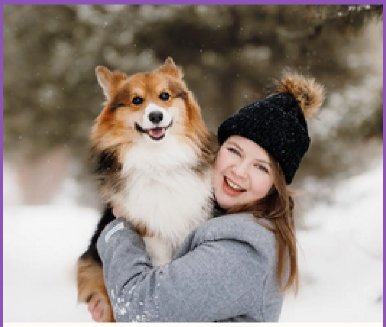
It is my first issue to be the co-editor-in-chief and I am really proud to present this edition of the Gene Zine. This issues covers a plethora of topics in personalised medicine - there will definitely be one that really interests you. I hope you will enjoy it.

I have really enjoyed working with the team - writers, editors, the newly added role of illustrators, and of course my partner, Geetika. A huge thank you to all of the hard work made to make this happen and looking forward to future issues of Gene 'Zine.

MEET THE EDITORS

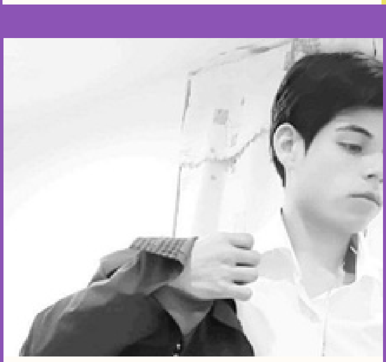
Corenna Twiss

Hi I'm Corenna and I'm a second year Biomed at New College! I love being a part of Gene 'Zine as I love the possibilities of personalised therapies, especially in relation to neuroscience!!



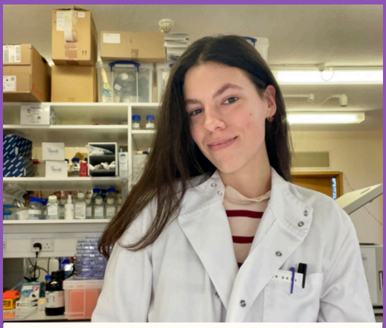
Courtney Yotter

Hello, my name is Courtney Yotter and I am originally from Seattle, Washington. I am in my first year at Hertford College reading for a DPhil in Psychiatry, focusing on different modalities to assess the brain's response to insulin, as means to advance our understanding of the relationship between poor insulin metabolism, diabetes, and cognitive disorders. Joining Gene 'Zine allows me to support cutting edge ideas and opinions that the student body is thinking about reach a wider audience. I am passionate about neurodegenerative diseases and the advancement of genotyping as a means to inform individuals on their risk of development of these conditions and ways they can decrease that risk through modifiable life factors, pharmaceutical targeting, and neuromodulation.



Efrain Uh

Efrain Uh is a graduate student reading for the MSc in Nanotechnology for Medicine and Health Care at the University of Oxford. As an aspiring Health Policy Analyst and Regulatory Affairs Specialist, Efrain is on a lifelong journey attempting to better understand how to align healthcare products, services, and strategies as well as human rights, intellectual property, and public health objectives.



Iulia Kis

I am Iulia, a 2nd year Oncology DPhil student at Keble College. My research focuses on DNA damage and repair, so most days you can catch me running around the lab trying to keep cells alive, but apart from this I am also very passionate about science communication and public engagement. Before joining the University of Oxford, I received a BSc in Medical Biosciences from Imperial College London, where I became lead editor of the Bioscience Review and developed a deep passion for science writing. Contributing to Gene 'Zine blends together my research focus, which relates to personalised cancer treatments to avoid therapy resistance, and my enthusiasm for the dissemination of scientific findings.

MEET THE EDITORS

Jenusiya Jeyaseelan

Hi! I'm a 2nd year Biochemist studying at Lady Margaret Hall. I'm interested in personalised medicine because of the breath of its application to healthcare and more specifically, its role in rare diseases. This opportunity will help spread awareness about ground-breaking research and treatments.

Larissa Chan

Hello! I am Larissa, a second-year undergraduate Biology student at St Hilda's College, Oxford. I joined Gene 'Zine as a writer and editor because I think that personalised medicine is a hugely intriguing field with a lot of promise and innovation. I'm very excited to contribute, edit, and be a part of a wonderful team!

Lloyd Kasper Shail

Wadham College, Medicine

Personalised medicine has the potential to revolutionise the insight we have into our own health and the decisions we will make when unwell. However, as with any new technology, it is incumbent upon us to consider the potential pitfalls it poses, alongside the obvious benefits. Currently my primary interest is likely to be ethics behind the gathering and use of our health data.

Luba Maslej

Luba is a Canadian first year DPhil student in women's and reproductive health, at Wolfson college. Her research focuses on exploring the immune mechanisms underlying endometriosis, a largely understudied reproductive disorder that significantly impacts the lives of those affected. In addition to endometriosis, Luba is interested in the broader variability of women's health and fertility, recognizing that this variability makes personalized medicine a promising approach to improving outcomes for women. These interests are what motivated her to be a writer and editor for Gene 'Zine.

MEET THE EDITORS

Yifei Zhou

Hi! Yifei here from Shanghai, a first year studying biomed at St John's college. Interned at a Nobel Laureate Lab last summer, looking at social isolation in fruit flies and multimodal sensory circuitry. Huge fan of museum and theatre. So, if you ever want to chat about anything remotely related to brain, cognition, literature, and art, or just play frisbee, erg, tennis, badminton, I'm game!

Yiran Wang

My name is Yiran and I'm a second-year Biomedical Sciences undergraduate at Lincoln College. My interests lie in topics such as neurological diseases and neural codes. I've also recently developed a keen passion in early mammalian development. I became a part of Gene 'Zine as a writer, but now I'm taking on the role of an editor to explore more about personalised medicine in areas other than neuroscience.

MEET THE WRITERS

ALIAA GAMAL

Aliaa is a passionate scholar, educator, and changemaker at the intersection of clinical pharmacy, sustainability, and global health. As a teaching assistant at the Faculty of Pharmacy and a master's student in Clinical Pharmacy, she blends academia with action, leading one of the largest community service initiatives in Upper Egypt.

A researcher at the Center for Research and Sustainability at Deraya University and a medical writer at Marvel Agency, Aliaa has spearheaded numerous clinical studies and published a series of cross-sectional and meta analyses. With an insatiable curiosity for global health policies, she strives to intertwine the medical world with the political frameworks of the SDGs and WHO aspirations.

BELISSA SCHERER FERNANDEZ

Hello! I'm Belissa, a sixth-year medical student at Ternopil National Medical University in Ukraine. I graduated Magna Cum Laude with a Bachelor's degree in Medical Biology from the University of South Dakota, USA, and pursued a degree in Neuroscience at the University of Barcelona, Spain. I also completed 18 months of U.S. Clinical Experience (USCE) in Houston, Texas. I am passionate about neurodegenerative and neurogenetic diseases, as well as advancing medical approaches to tackle brain dysfunction. I joined Gene's Zine to share my insights and ignite a deeper curiosity about brain health. My goal is to spark interest about the latest advancements in medicine for treating brain disorders. I hope these insights captivate and inspire you!

CORENNA TWISS

Hi I'm Corenna and I'm a second year Biomed at New College! I love being a part of Gene 'Zine as I love the possibilities of personalised therapies, especially in relation to neuroscience!!

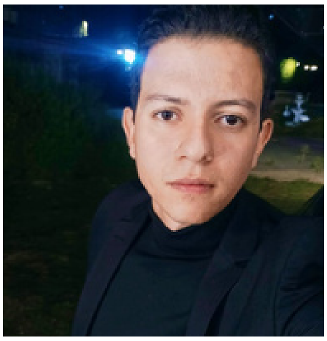
EFRAIN UH

Efrain Uh is a graduate student reading for the MSc in Nanotechnology for Medicine and Health Care at the University of Oxford. As an aspiring Health Policy Analyst and Regulatory Affairs Specialist, Efrain is on a lifelong journey attempting to better understand how to align healthcare products, services, and strategies as well as human rights, intellectual property, and public health objectives.

HANNAH SANDHU

I'm Hannah, a second-year Biomedical Sciences undergraduate at Keble College. I have a particular interest in how microRNAs can transform personalised diagnosis and treatment- especially in oncology and cardiovascular research. My past work includes a review on enhancing glioblastoma therapy by targeting temozolomide resistance with miRNA modulation, as well as recent research using miRNA tools and spatial transcriptomics to improve diagnosis and treatment of HFrEF. I'm fascinated by the future of cancer immunotherapy, the promise of PROTACs in precision oncology, and the growing role of AI in clinical practice. I'm eager to explore and share new ideas at the intersection of research and innovation through Gene'Zine.

HOSSAMELDIN SABER AHMED



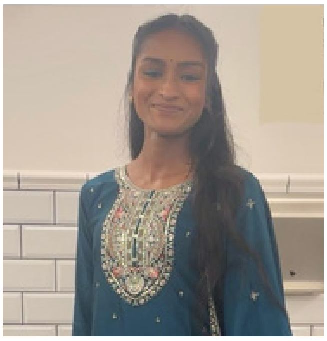
I'm a MSc student of Clinical Epidemeology with interest in personalized medicine and Pharmacogenomics.
Enthusiast with medical writing and introducing evidence based science to healthcare workers and the public.

MEET THE WRITERS

ISABEL ITOE

My name is Isabel, and I'm a second year Biochemist at Queen's! My interest in personalised medicine began with a desire to understand how the gut microbiome affects the body and how this information can be manipulated to provide personalised treatments for different diseases. I am also interested in inflammation and how it affects our mental and physical health. I am looking forward to writing for Gene 'Zine because I believe that science writing is a powerful tool that can be used to connect people from different disciplines and drive social change! In my free time I write creatively and play the piano.

JENUSIYA JEYASEELAN



Hi! I'm a 2nd year Biochemist studying at Lady Margaret Hall. I'm interested in personalised medicine because of the breath of its application to healthcare and more specifically, its role in rare diseases. This opportunity will help spread awareness about ground-breaking research and treatments.

JESSICA SCHERER FERNANDEZ

Hi! I'm Jessica. I graduated Magna Cum Laude with a Bachelor's degree in Medical Biology from the University of South Dakota, USA, and hold a Master's degree in Neuroscience from the University of Barcelona, Spain. Currently, I'm in my sixth year as a medical student at Ternopil National Medical University in Ukraine. I've completed 18 months of U.S. Clinical Experience (USCE) in Houston, Texas, and am undertaking elective placements in Oxford, UK. I joined Gene's Zine as a writer to share my passion for medical advancements in neuroscience, especially neurodegenerative diseases and rare genetic conditions.

JULIUS BULLO

I am passionate about the transformative potential of personalised medicine, with a particular interest in its applications to cancer care and infectious diseases. I am an MCR Associate student at Magdalen College and a 6th-year medical student with the NDCM, affiliated with Ivan Horbachevsky Ternopil National Medical University in Ukraine. As part of my final year, I am completing clinical training with Oxford University Hospitals NHS Trust, based at the JR Hospital and the Churchill Hospital. Prior to studying medicine, I undertook postgraduate studies in Genomic Medicine at the University of Exeter. I received specialised training in microbial genome sequencing at Harvard Medical School in Boston, USA, and in genetic data analysis at the University of Cambridge.

LARISSA CHAN

Hello! I am Larissa, a second-year undergraduate Biology student at St Hilda's College, Oxford. I joined Gene 'Zine as a writer and editor because I think that personalised medicine is a hugely intriguing field with a lot of promise and innovation. I'm very excited to contribute, edit, and be a part of a wonderful team!

LAUREN LAUGHLIN

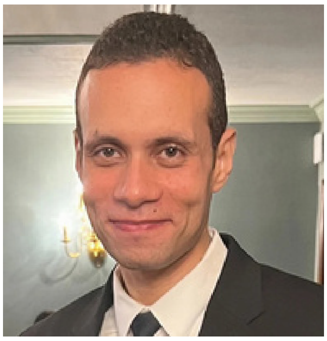
Hi! I'm Lauren, a second year undergrad studying biomedical sciences at Exeter College. I'm super excited to join the Gene 'Zine so I can further explore (and share!) my interests in personalised medicine - particularly looking at how variance in certain genes can confer susceptibility to various diseases, as well as influencing the patient's response to treatments. This is important in re-framing how we approach preventing, diagnosing, and treating these diseases, centred around the individual patient and their unique genetic makeup.

MEET THE WRITERS

LUCY ROBINSON

Hi, my name's Lucy and I'm a second year undergraduate at St Edmund Hall studying Biomedical Sciences. I was keen to be part of the Gene 'Zine team because I'm very interested in how global issues, such as cancer and antibiotic resistance may be approached at an individual level, to improve both individual patient outcomes and be part of the solution to wider problems in public health.

MAZHAR ELSHORBAGI



Mazhar ElShorbagi works as a Scholar of Political Philosophy and the International Cooperation Focal Point at Deraya University. He teaches philosophical and critical thinking, bioethics, and the philosophical aspects of health to undergraduate and postgraduate students of life sciences disciplines. His scientific conviction is that if the sciences enable us to know how to progress, the humanities act as our compass in determining the ethical and logical patterns to implement such progress. He believes that scientific writing is a crucial way to stimulate curiosity and raise questions that will enrich scientific life.

NANDINI KAPOOR

Hi! My name is Nandini and I'm a post-graduate student at Wolfson College. I'm pursuing an MSc in Evidence-Based Social Intervention and Policy Evaluation. I'm passionate about how personalised medicine can design targeted treatments, as well as exploring the social and ethical implications of this emerging technology. I'm excited to contribute to Gene 'Zine and have the opportunity to delve deeper into these interests through my writing!

VIVIEN KAREN MOK

Hi, I'm Vivien and I am currently a second year Biomedical Science undergraduate at King's College London. My passion lies in enhancing the quality of life for those facing health challenges. Through this objective, I have found interest in personalised medicine, specifically in the prospect of developing biotechnology that can improve the experience of surgical interventions for people with hearing loss. As a former medical writer, I enjoy writing about ongoing scientific and medical research, and Gene 'Zine offers the perfect opportunity for me to showcase the direction in which I strive to learn and grow.

YASMIN HAMDY

Yasmin is a Scholar at the Boutros-Ghali Chair for Sustainable Peace, a non-resident Fellow at the Arms Control Negotiation Academy, a Fellow at the Africa Climate Mobility Academy, and a Part-time Scholar at Deraya University's Center for Research and Sustainability. She served as a Reviewer at the Oxford University COVID-19 Government Response Tracker. She studied Medicine Development at King's College London. Yasmin obtained a bachelor's degree in pharmacy with distinction from Deraya University. Her main passion for scientific journalism is to upgrade young people's mindsets in the context of life science. She was awarded as a UNHCR Young Champion for Refugees and named a Young Arab Pioneer from the Arab Youth Center in the UAE.

ZEHRA AZIM

Pursuing an MSc in Integrated Immunology at Hertford College, I'm thrilled to be part of Gene 'Zine. I joined Gene 'Zine because it offers an exciting platform to stay at the forefront of personalised medicine developments, engage with cutting-edge research, and contribute to discussions that could shape the future of healthcare. As an aspiring immunologist, I'm eager to explore how immunological insights can inform tailored therapeutic approaches and share these discoveries with the Gene 'Zine community.

SHRIKANT VERMA

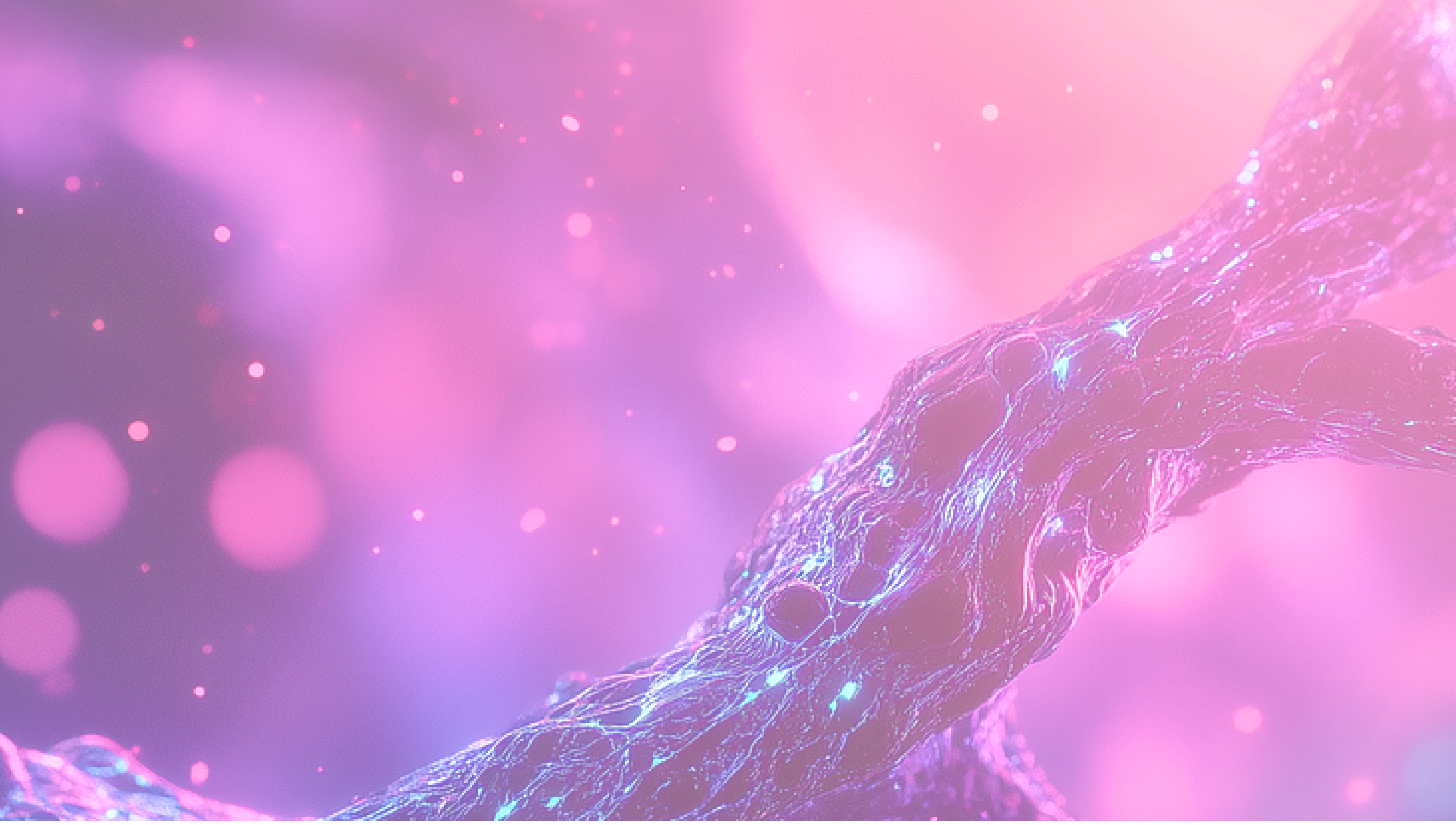
MEET THE ILLUSTRATOR

HONOR DAVIES

Hi, I'm Honor and I'm a second-year undergraduate biochemist at Queen's College! My interest in personalised medicine lies primarily in neurodegenerative disorders, and PM's applications to cancer immunotherapy, including personalised neoantigen vaccines and the long-lasting memory potential of neoantigen specific T cells. I applied to Gene 'Zine as I'm fascinated by how tailored approaches can be applied to treatment-resistance patients to improve their quality of life as part of this innovative field. I joined as an Illustrator as I love bringing complex ideas and paragraphs of text to life through illustration, making cutting edge research more accessible to a wider audience in a creative way. In my spare time, I also enjoy film and creative writing!

IZZI REID

Hi! I'm Izzi, a 2nd year Biomedical Sciences student from St Anne's. I joined the team because I think personalised medicine has the potential to help develop effective therapies for complex diseases and improve treatment accessibility. I've always loved drawing, so illustration is an exciting way to communicate ideas about science - I hope my work is not just fun to look at, but that it sparks interest in both medicine and art!



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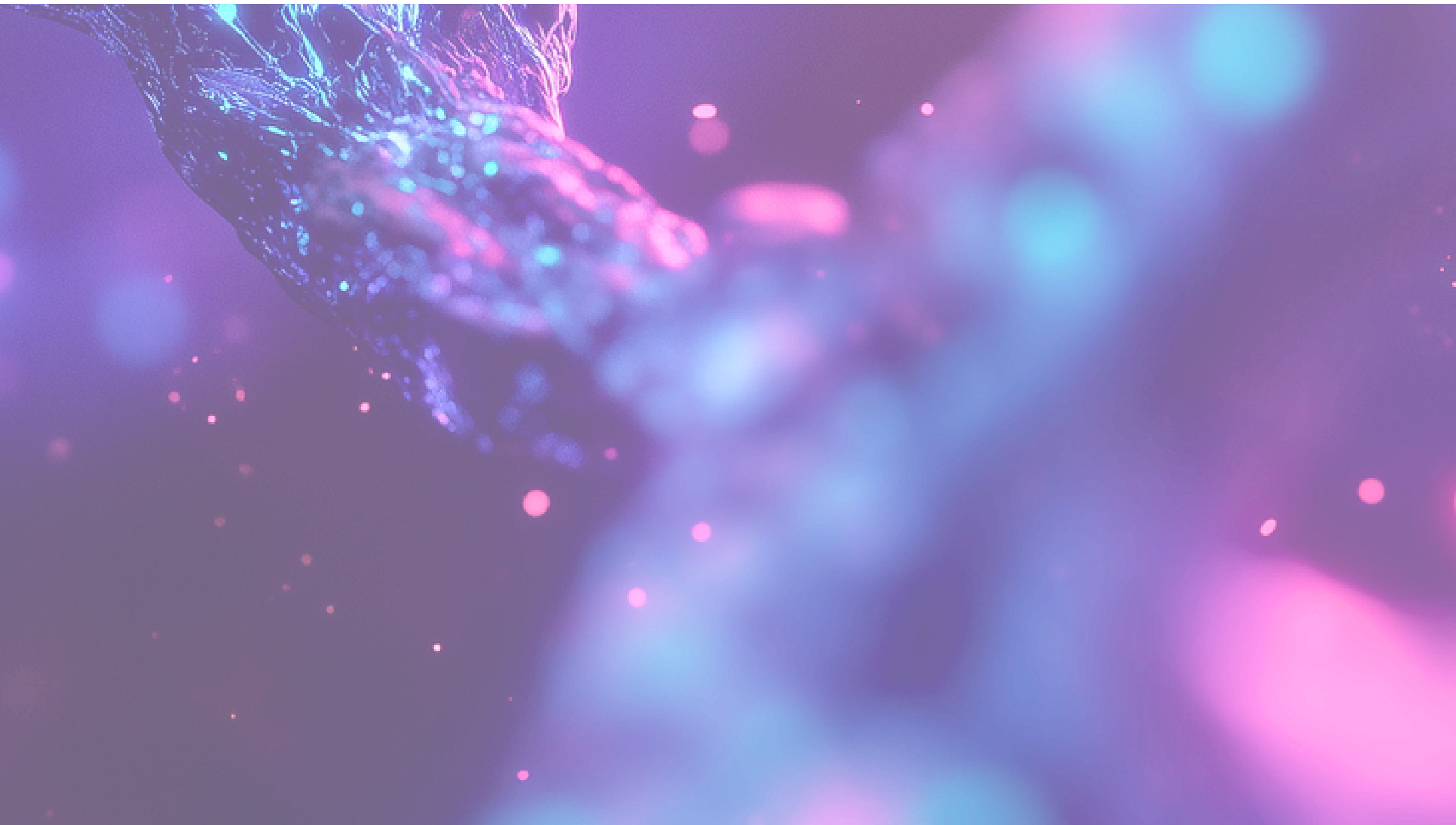

Menstrual Stem Cells: The Therapeutic of the Future?

by Corenna Twiss

Stem cells are a prospect that has been explored with great optimism in recent years and their immense potential for therapeutic applications is widely recognised. However, as with many scientific advances, there is also a great amount of controversy in this field – most specifically surrounding the ethically contentious use of embryonic stem cells. However, recent discovery of menstrual-derived stem cells (MenSCs) provides an abundant, non-invasively accessed and ethically-sound source of stem cells that are under investigation for their therapeutic benefit(s).

The notion to investigate menstrual blood for stem cells was inspired by the intrinsically replicative and regenerative nature of the uterine lining. The lining of the uterus is functionally divided into the basalis and the functionalis. The basalis is the deeper layer that contains the MenSCs and is maintained throughout the menstrual cycle. The functionalis is the layer that is shed during menses and is subsequently regenerated by the MenSCs that reside within the basalis. Although the MenSCs are not typically found in the functionalis itself, they are still present in the uterine content that is shed during menses. This is because there is disruption of the layers and vascularisation of the uterine lining during menses, which results in some MenSCs being lost in the menstrual blood. These menstrual-derived stem cells fall under the category of mesenchymal stem cells, meaning they are multipotent and have the ability to differentiate into a number of different cell types, including bone cells, muscle cells and more. Crucially, due to their menstrual source: (1) these stem cells are frequently and abundantly available, (2) can be collected easily without invasive intervention, and (3) don't have any of the ethical concerns associated with embryonic stem cells. Therefore, if they can be utilised for therapeutic benefit, these cells could revolutionise the stem cell and personalised medicine fields.

MenSCs in stem cell therapy

A key concept of stem cell therapy is that of immunogenicity. This describes how a foreign molecule or tissue introduced into the body may initiate an immune response. Therefore, in the case of stem cell therapy, there is little to no benefit in introducing cells that are immediately destroyed. Notably, high immunogenicity of introduced cells could trigger an immense immune response within the body, potentially causing organ damage and leaving a patient in worse health than they were initially. Therefore, the risk that a stem cell introduced into the body could induce an immune response is a pertinent one and the fact that experiments have demonstrated menstrual stem cells to have a low immunogenicity lends them to having great therapeutic promise.

Menstrual stem cells can be therapeutically useful in a range of conditions either by differentiating into functional cells or by modulating the extracellular environment through the cytokines and other signalling molecules they release (paracrine effects). These paracrine factors can drive tissue repair, cellular protection or immunomodulation. The potential therapeutic benefits of these cellular mechanisms have been investigated with respect to wound healing, cancer, neurological diseases and many more. Their diverse morphological potential and wide applicability make menstrual stem cells a prime research avenue for personalised medicine as they have the potential to be manipulated to aid the specific needs of an individual's disease state.

Could menstrual stem cells cure neurodegenerative disease?

Alzheimer's Disease (AD)

One main focus of menstrual stem cells research has been that of AD research. AD is characterised by the development of beta-amyloid plaques, and tangles formed from tau, within and between the neurons in the brain. This pathology ultimately leads to the death of the neurons and the subsequent neurological deficits. Recent studies into the potential applications of menstrual stem cells have been conducted in mouse models of AD (mice manipulated to express genes often associated with familial AD). Fascinatingly, the transplantation of MenSCs into the brain of these mice resulted in a number of neuroprotective mechanism, including: activation of microglia (brain immune cells) to assume a phenotype that results in increased activity of enzymes associated with the degradation and clearance of beta-amyloid and a reduction in the rate of protein deposition. Furthermore, there was a reduction in the abnormal APP (Amyloid Precursor Protein) processing that is seen in AD, which is the process that results in the formation of the misfolded beta-amyloid. A second hallmark of AD is that of neurofibrillary tangles made of the protein tau. This study also provided evidence for the theory that the transplantation of MenSCs into the brain could reduce the hyperphosphorylation of this tau protein.

This is crucial, as it is this hyperphosphorylation that is believed to assist in driving the aggregation of this protein into the pathological tangles, and hence the alleviation of this hyperphosphorylation reduces this pathological effect. This research has demonstrated that transplantation of menstrual stem cells into the brain can result in improvements in the learning and memory abilities of the mice and subsequently this area of research shines light on the possibility of MenSCs to aid in AD treatment.

Parkinson's Disease (PD)

The therapeutic ability of MenSCs is also shown to extend to PD. In a study that introduced MenSCs to the brains of PD model mice, there was shown to be an improvement in the motor function, specifically a greater movement distance, which could possibly be attributed to the associated drop in the loss of dopaminergic neurons and the reduction in pro-inflammatory molecules seen in the body as a result of the MenSC therapy. It is clear that if this could be translated into human therapies, this could have a startling effect on the quality of life and progression of the disease experienced by PD patients.

Other MenSC applications

One fascinating branch of research exploring menstrual stem cells' therapeutic potential is in their ability to differentiate into cardiomyocytes. One experiment demonstrated that when MenSCs were cultured together with cardiomyocytes, approximately 50% of the MenSCs began beating within 5 days and around 30% of them were subsequently shown to have differentiated into cardiomyocytes. This ability to assume the beating property that is so characteristic of muscle cells is a fascinating demonstration of the potential of MenSCs and raises the idea of applications of these to cardiac muscle regeneration following myocardial infarction.

Challenges of MenSC therapy

There are a number of limitations to MenSCs including the fact that heterogeneity between donors may influence the biological properties of these MenSCs and hence these cells may not always behave predictably. Additionally, although highly proliferative, MenSCs don't have limitless morphological potential and it is not possible for them to differentiate into all possible cell types. Finally, while many of the studies in this field show remarkable potential, it is important to remember that a large proportion of these studies are still at the stage of mouse models and hence these are very early breakthroughs that may not necessarily translate into human therapeutics.

Conclusion

Despite these limitations, MenSCs show remarkable potential within an extensive range of clinical applications. Hence, the ongoing research into their therapeutic benefit is an area of great interest and is one that highlights the importance of thinking outside the box. Furthermore, the immense and diverse lineage potentials of MenSCs and the vast number of conditions they have already shown promise in lends these cells to personalised medicine as they have the ability to provide specific therapeutic benefit tailored to the pathological state.

References & Further Reading

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REWIRING THE MIND: NEUROMODULATION IN LEWY BODY DEMENTIA CARE

By Belissa Scherer Fernandez

Lewy Body Dementia (LBD), a progressive neurodegenerative disorder second only to Alzheimer's disease in prevalence, affects approximately 0.4% of the global population and accounts for 5–10% of all dementia cases worldwide. It continues to challenge clinicians with its complex clinical picture of cognitive fluctuations, parkinsonism, visual hallucinations, and neuropsychiatric symptoms. Current pharmacological options, including cholinesterase inhibitors and antipsychotics, offer modest symptomatic relief but are frequently accompanied by intolerable side effects and do not alter disease progression.

Amid this therapeutic void, neuromodulation techniques-ranging from invasive deep brain stimulation (DBS) to non-invasive transcranial magnetic stimulation (TMS)-have emerged as innovative, circuit-based interventions. These approaches hold promise not merely for symptom management but potentially as disease-modifying therapies tailored to the individual neurophysiological profile of each patient. In this article, we explore the latest evidence on neuromodulation in LBD care and its implications for the future of personalized dementia medicine.

The Rationale for Neuromodulation in LBD

Lewy Body Dementia is characterized by pathological inclusions of α-synuclein within neurons, leading to disrupted neurotransmission across key cognitive and motor networks. Of particular interest is the degeneration of the nucleus basalis of Meynert (NBM)-a major cholinergic nucleus critical for attention and memory. Restoring activity within this and other implicated networks via neuromodulation has been postulated as a potential therapeutic strategy.

Zhang (2015), author of *Disease-modifying therapeutic directions for Lewy-Body dementias,* aptly outlined the unmet need for disease-modifying treatments in LBD, identifying network dysfunction and neurotransmitter deficits as actionable targets for novel interventions, including neuromodulation therapies.

The innovative therapeutic strategies target reducing alpha-synuclein levels to prevent its toxic effects on neurons, inhibit cell-to-cell transmission to limit the progression of neurodegeneration and neuromodulation therapies such as deep brain stimulation, to restore network function and improve symptoms in LBD patients. These emerging therapies represent a shift towards disease-modifying treatments that target the root causes of LBD, offering hope for more effective management of this complex neurodegenerative disorder.

Deep Brain Stimulation: Targeting the Nucleus Basalis of Meynert

Among invasive techniques, deep brain stimulation of the NBM has gained increasing attention for its potential to enhance cognitive function in neurodegenerative dementias.
Deep Brain Stimulation (DBS) is a surgical procedure that involves implanting electrodes into specific areas of the brain to deliver controlled electrical impulses. These impulses modulate abnormal neural activity, aiming to restore more typical patterns of brain function.
Gratwicke *et al.*, (2020) conducted a pioneering randomized clinical trial evaluating bilateral NBM DBS in patients with dementia with Lewy bodies (DLB), a clinical entity within the LBD spectrum. The study reported encouraging improvements in attentional performance and daytime alertness, although neuropsychiatric side effects and heterogeneity in response underscored the need for further refinement in patient selection and stimulation parameters.

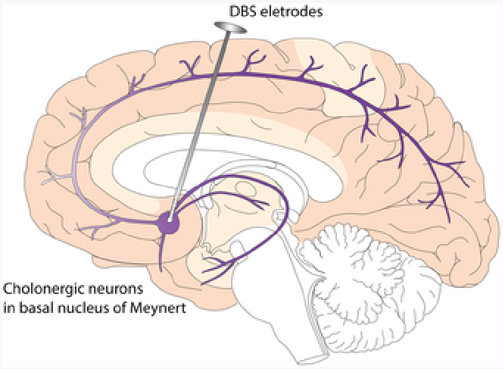

Fig 1. *Deep Brain Stimulation (DBS) of Nucleus Basalis of Meynert (NBM) in Dementia with Lewy Bodies (DLB). Frontier Neuroscience.*

Complementing these findings, Maltête et al., (2021) demonstrated in an open-label study that NBM DBS improved neuropsychiatric symptoms, particularly hallucinations and agitation, in individuals with LBD, providing further impetus for this targeted approach.

Studies such as Deep brain stimulation for dementias comprehensively reviewed the role of DBS in dementias, emphasizing that while the therapeutic window remains narrow, the technique's ability to modulate dysfunctional circuits holds significant potential, especially when guided by personalized connectomic data.

Non-Invasive Neuromodulation: TMS and Hallucination Control

Transcranial Magnetic Stimulation (TMS) is a non-invasive technique that uses magnetic fields to stimulate nerve cells in specific brain regions. It has been explored as a potential treatment for various neurological and psychiatric conditions, including LBD.

Thus, transcranial Magnetic Stimulation (TMS) is a promising treatment for Lewy Body Dementia (LBD) as it targets multiple aspects of the disease's pathophysiology. By enhancing cortical excitability in underactive regions like the dorsolateral prefrontal cortex (DLPFC), TMS can improve cognitive function. It also modulates neurotransmitter systems by increasing dopamine release in the striatum, boosting cholinergic activity, and normalizing GABA/glutamate imbalances, which helps restore inhibitory-excitatory balance disrupted by α-synuclein pathology. Additionally, TMS may strengthen network connectivity through improved synaptic plasticity and reduce neuropsychiatric symptoms such as depression and hallucinations.

According to the article *Visual hallucinations in dementia with Lewy bodies: transcranial magnetic stimulation study applied TMS to investigate the neurophysiological underpinnings of visual hallucinations in DLB,* the study revealed that increased excitability in the occipital cortex correlated with hallucination severity, suggesting that targeted neuromodulation might alleviate one of the most distressing symptoms of LBD.

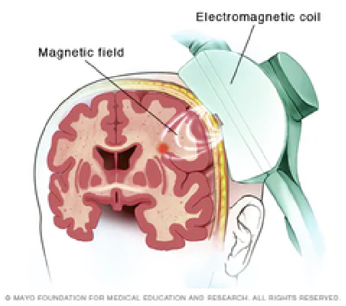

Fig 2. *Mayo Clinic-Transcranial Magnetic Stimulation (TMS).*

Looking Beyond: Personalized Neuromodulation in Neurodegenerative Disease

While direct clinical trials in LBD are limited, recent advances in neuromodulation for Alzheimer's disease illustrate the broader potential of personalized, circuit-based interventions. In a recent Phase 2 study, Sinaptica Therapeutics reported that non-invasive, personalized neuromodulation targeting the Default Mode Network significantly slowed cognitive decline over 12 months in individuals with Alzheimer's disease—a compelling proof of concept for individualized neuromodulation strategies in dementia care.
These findings reinforce the premise that precise targeting of disease-affected neural networks, guided by structural and functional neuroimaging, could transform management paradigms not only in Alzheimer's but also in related dementias such as LBD.

As pharmacological therapies reach their limits in treating Lewy Body Dementia, neuromodulation offers a hopeful frontier. Techniques such as deep brain stimulation of the nucleus basalis of Meynert and transcranial magnetic stimulation of the occipital cortex are beginning to demonstrate clinical utility, with early studies showing benefits in cognitive function, alertness, and neuropsychiatric symptoms.

The future of LBD care likely lies in personalized neuromodulation-leveraging patient-specific connectomics and symptom profiles to guide targeted interventions. As this field advances, it promises not only symptomatic relief but perhaps the long-sought goal of disease modification in this devastating disorder.

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BREAKING THE SEIZURE CODE: GENE EDITING AND ADVANCES IN CHILDHOOD EPILEPSY

By Jessica Scherer Fernandez

Epilepsy affects around 1% of the global population and child prevalence is estimated at around 0.5% to 1%, with roughly 30% of patients being drug-resistant and left with limited treatment options. While newer antiseizure medications have been developed, their impact on these drug-resistant cases remains modest. Considering this, gene therapy and gene editing - particularly CRISPR-based methods - are emerging as powerful therapeutic strategies. Several gene-editing clinical trials are already underway or in development, signaling a new era in epilepsy treatment.

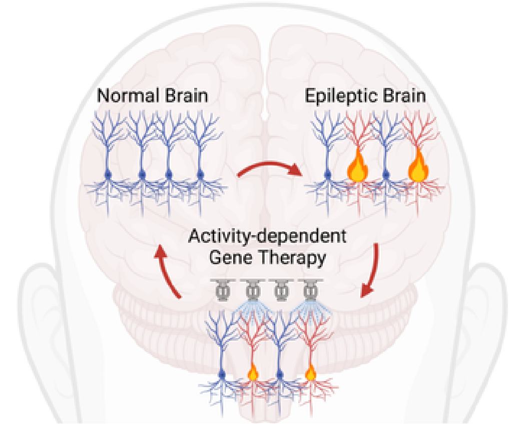

Fig 1. *Gene Editing in Epileptic Seizures*

The Genetic Puzzle of Childhood Epilepsy

Genetic factors are responsible for 70–80% of epilepsy cases, including many rare monogenic forms caused by de novo mutations. Approximately 1,000 epilepsy-related genes have been identified, with mutations in ion channels accounting for about 25% of monogenic cases. Other common targets include genes involved in synaptic transmission, brain development, and metabolism. Epilepsy incidence is highest before age five, and a small group of genes—such as SCN1A, KCNQ2, and CDKL5—account for approximately 80% of monogenic epilepsies. These often lead to developmental and epileptic encephalopathies (DEEs), marked by severe seizures and neurodevelopmental delays, and are frequently drug-resistant. Because of their severity, DEEs are prime candidates for gene-based treatments. Still, various gene editing tools offer paths to correction depending on the mutation's mechanism, such as loss-of-function, gain-of-function, or dominant-negative mutations. Childhood epilepsies, especially severe forms such as Dravet syndrome or Lennox-Gastaut syndrome, are frequently linked to mutations in specific genes regulating neuronal excitability. Until recently, the best clinicians could offer were antiepileptic drugs—often a trial-and-error process with limited success. But as our understanding of the genetic underpinnings of epilepsy deepens, so too does our ability to intervene at the root cause.

In a pivotal review, *Unraveling the Genetic Basis of Epilepsy* (2024), researchers emphasized that hundreds of genes are now implicated in various forms of epilepsy. This complexity, though daunting, provides opportunities: each mutation is a potential target for highly tailored therapy.

Gene Therapy Discoveries: From Laboratory Research to Clinical Application

The idea of correcting disease at the genetic level once belonged to science fiction, which is no longer the case. In fact, gene therapy for epilepsy is already moving into clinical development. As detailed in *Recent Advances and Current Status of Gene Therapy for Epilepsy* (2024), state-of-the-art strategies include gene replacement, antisense oligonucleotides (ASOs), and viral-vector mediated gene modulation. Clinicians can treat epilepsy by replacing or modifying defective genes that contribute to seizures. Moreover, ASOs can be used to target specific mRNA molecules, either silencing overactive genes or correcting mRNA splicing to restore normal neuronal function. Additionally, viral vectors are used to deliver therapeutic genes to brain cells, aiming to replace defective genes or adjust gene expression, ultimately reducing neuronal excitability and preventing seizures.

Another striking discovery was reported by the Queen Square Institute of Neurology, University College London. Researchers have developed a promising gene therapy for treating focal cortical dysplasia, a common cause of drug-resistant epilepsy in children. The therapy, which involves overexpressing a potassium channel to regulate neuronal excitability, significantly reduced seizures in mice by 87%, without affecting memory or behavior. This approach offers a potential alternative to risky brain surgery and is expected to undergo clinical trials in the next five years, with hopes to benefit thousands of children currently suffering from uncontrolled seizures.

CRISPR/Cas9 and Precision Medicine

CRISPR-Cas9 is a groundbreaking gene-editing technology that enables scientists to precisely modify DNA within living cells, offering hope for treating genetic forms of epilepsy. The system is adapted from a natural defense mechanism found in bacteria, where it is used to cut viral DNA. In the laboratory, researchers design a small piece of RNA called a guide RNA (gRNA) that matches the specific DNA sequence they want to target—such as a faulty gene causing epilepsy. This gRNA directs the Cas9 enzyme to that exact spot in the genome, at which Cas9 acts like molecular scissors, cutting both strands of DNA. After the cut is made, the cell naturally attempts to repair the break. During this repair process, scientists can either disrupt the faulty gene to silence it or insert a healthy version of the gene using a DNA template.

Complementing these findings, Gene Editing and Modulation: The Holy Grail for the Genetic Epilepsies describes how CRISPR-Cas9 could be used to fix mutations in genes like SCN1A, which are responsible for producing proteins that regulate electrical activity in the brain. Scientists elicited CRISPR activation to upregulate the expression of the healthy SCN1A allele, resulting in improved seizure control in animal models. While these methods are still largely experimental, preclinical studies have shown dramatic seizure reduction in animal models.

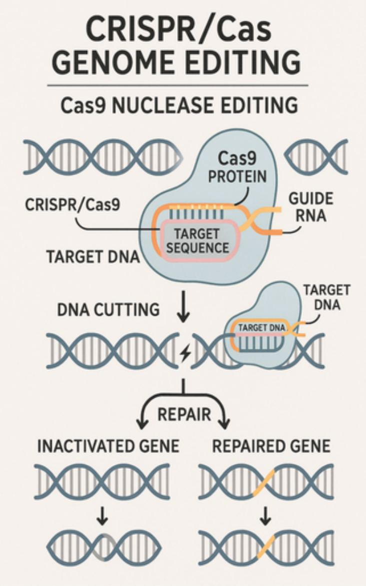

Fig 2. *CRISPR-Cas9-mediated Adaptive Immunity Mechanism*

Challenges on the Horizon

Gene therapy is not without risks. Delivery to the brain poses technical hurdles, and the ethical considerations surrounding gene editing, especially in children, require careful navigation. Additionally, as Gene Therapy for Epilepsy in the Handbook of Clinical Neurology outlines, the immune response to viral vectors, long-term safety, and affordability all leave open questions. Limitations include inefficient CNS delivery, low editing efficiency, immune responses, overcoming the blood-brain barrier and genetic mosaicism. Moreover, balancing neural activity and timing therapeutic intervention is crucial in managing epilepsy. Mutations in ion channels can alter neuronal excitability, affecting therapeutic responses. The timing of interventions is critical, with early treatments being more effective in some conditions like Angelman Syndrome.

Nevertheless, the therapeutic potential is too significant to ignore. Gene editing offers a versatile and powerful approach to treat the full range of mutations underlying genetic epilepsy. By harnessing precision medicine, clinicians can move away from broad-spectrum medications and toward targeted, mechanism-based interventions.

The Future: A Genetic Map to Healing

The progress is real, though the journey is far from over. As gene therapy enters human trials and editing tools grow more precise, the goal of curing epilepsy, not merely controlling it, seems achievable. For families affected by genetic epilepsies, the idea of decoding and correcting the mutation behind a child's seizures is no longer a distant hope—it is becoming a tangible reality.

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THE BIDIRECTIONAL RELATIONSHIP BETWEEN DEPRESSION AND INFLAMMATION AND POTENTIAL FOR PERSONALISED TREATMENTS

By Isabel Itoe
With illustration by Honor Davies

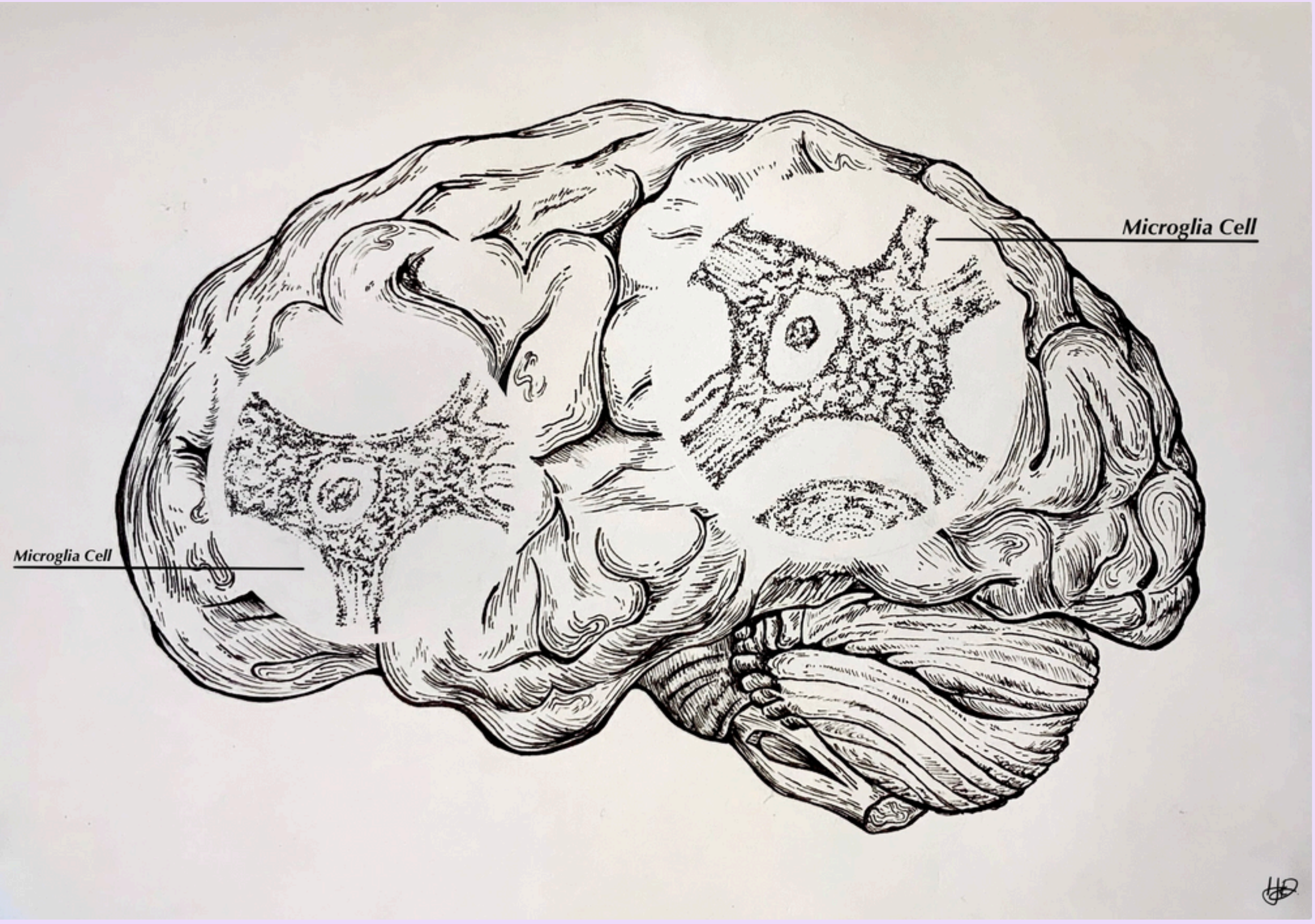

Fig 1. *Microglia play a fundamental role in modulating neuroinflammation, and could be involved in pathogenesis of depression.*

Introduction

Since the 1960s, when doctors first observed that serotonin-boosting drugs improved mood, the serotonin theory of depression has dominated discourse around the cause of the disorder. But with this theory coming under recent scrutiny, alternative theories about the pathogenesis of depression are gaining momentum, one of which centres around the bidirectional relationship between inflammation and depression. If inflammation plays a key role in the pathogenesis of the disease, can this information be harnessed to develop personalised immunotherapies to treat depression?

What is Depression and What Causes It?

Major Depressive Disorder (MDD) is characterised by chronic low mood; feelings of hopelessness and helplessness; and a loss of interest in activities that once brought joy. Since the 1960s, the main cause of depression has been thought to be a “chemical imbalance”, with the theory that depressed individuals have lower levels of brain serotonin governing the public’s perception of the disorder. This concept was coined in the 1960s when doctors observed that iproniazid, a drug known to elevate serotonin levels, improved the mood of patients. Their observations were supported by the fact that Serotonin Selective Reuptake Inhibitors (such as Fluoxetine, more commonly known as Prozac) could be used to treat depression; these drugs block the reuptake of serotonin from synapses, leaving synaptic levels of serotonin higher and improving mood.

However, in 2022, The Moncrieff Review, which collated a variety of evidence related to the serotonin theory of depression, concluded that “there is no convincing evidence that depression is associated with, or caused by, lower serotonin concentrations or activity”. Whilst this conclusion was disputed and led to a chaotic clash of academic theories, the disintegration of the chemical imbalance theory has given space for other theories to grow. If the theory that society has clung onto in a desperate attempt to make sense of a largely misunderstood disorder is wrong (or at the very least, highly disputed), what is the true cause of depression, and how can we use this to improve the lives of those suffering with the condition?

An interesting hypothesis is that chronic, low-level inflammation is a potential cause, as well as consequence, of the disorder. But with the current evidence suggesting that this may only apply to a specific group of patients, a blanket, one-size-fits-all approach is unlikely to work. Translating this theory into meaningful and effective treatment would require a tailored approach, suggesting that immunotherapy-based treatments of depression would work well within a personalised medicine framework of treatment.

The Cytokine Hypothesis of Depression

Inflammation is thought to play a central role in the pathogenesis of depression: depressed individuals have on average higher levels of pro-inflammatory cytokines, and depressive symptoms have been induced in hepatitis patients treated with IFN-gamma, a pro-inflammatory cytokine. This has given rise to the cytokine hypothesis of depression: that pro-inflammatory cytokines, such as Tumour Necrosis Factor alpha (TNFα), play a critical role in translating internal and external stressors into depressive symptoms. Neuroinflammation is particularly critical to the pathogenesis of depression, which involves the release of pro-inflammatory cytokines in the brain upon glial cell activation. Microglia and astrocytes, the immune cells of the central nervous system, are also heavily involved in modulating neuroinflammation.

How Does Stress Trigger Neuroinflammation?

Whilst stress can trigger neuroinflammation directly by stimulating the release of pro-inflammatory cytokines from microglia and astrocytes, the NLRP3 inflammasome and the HPA axis provide further explanations how stress can result in inflammation. In the case of the NLRP3 inflammasome, the connection between stress and inflammation is direct, with low levels of long-term stress activating the inflammasome, which causes it to release pro-inflammatory cytokines such as IL1β.

An upregulated HPA axis provides a more convoluted connection between stress and neuroinflammation, with stress-related stimuli first resulting in systemic inflammation, which is thought to activate neuroinflammation. This pathway is mediated by the hypothalamic-pituitary-adrenal (HPA) axis, which facilitates communication between the brain and the peripheral immune system. Stress stimulates the release of corticotropin-releasing factor (CRH) from the hypothalamus, which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH then stimulates the release of noradrenaline and adrenaline from the medulla of the adrenal glands, and glucocorticoid from the cortex of the adrenal glands; these two hormones activate immune cells and promote the release of pro-inflammatory cytokines. These pro-inflammatory cytokines can also activate the HPA axis, highlighting the bidirectionality of the relationship. This pathway is thought to be upregulated in depressed individuals, and it has been theorised that the resultant systemic inflammation can trigger neuroinflammation.

How Does Neuroinflammation Alter Mood?

The Cytokine Hypothesis of depression centres around the idea that inflammation is involved in translating external stress stimuli into depressive symptoms. This raises the question of how exactly neuroinflammation alters the neural circuits involved in the pathogenesis of depression. One plausible explanation for this could be that inflammation alters the reward circuit11, which is involved in stimulating a positive emotional response to certain behaviours. It is thought that this system goes awry in some depressed individuals, with the brain's ability to identify potential rewards hindered, and the identification of negative outcomes enhanced . This imbalance between perception of risk and reward is then thought to result in depression.

What Evidence Supports This Theory?

Studies show that higher levels of C-reactive protein, a biomarker for inflammation, correlates with reduced connectivity between the parts of the brain involved in this reward circuit. The effect of inflammation on the reward circuit is further supported by studies that demonstrate that inflammation-induced alterations to ventral striatum activity, which is part of the reward circuit, has a discernible impact on participants' behaviour towards reward and punishment11. For example, typhoid vaccination, which stimulates inflammation, distorted depressed patient's perceptions of reward and punishment, with the former becoming less desirable and the latter becoming more repulsive.

Potential for Personalised Treatments

The process of finding a medication that improves a patient's depressive symptoms can often be a long and demoralising one: it is difficult to know which medication will work, often leaving no other choice than to take a trial-and-error approach that can fuel pre-existing feelings of helplessness and fatigue. Taking a personalised approach, centred around determining which treatment is likely to work based on a patient's biomarkers and medical history, could be used to streamline an otherwise convoluted and exhausting pathway towards remission.

As well as helping healthcare professionals decide which of the current depression treatments would best fit the patient, with anti-depressants known to reduce inflammation being the ideal choice for patients with raised inflammatory markers, The Cytokine Hypothesis of depression opens the door for a variety of new personalised immunotherapies. These immunotherapies are centred around reducing unwanted inflammation – both systemic and neuroinflammation. Treatments could involve targeting pro-inflammatory cytokines such as Tumour Necrosis Factor Alpha (TNF-alpha) using anti-TNF-α antibodies such as infliximab; or targeting specific Toll-Like Receptors, some of which play roles in triggering inflammation and are upregulated in depressed individuals. The NLRP3 inflammasome is also a promising target, given the availability of appropriate inhibitors and evidence that reducing inflammation induced by NLRP3 inflammasome activation may be an effective treatment in individuals with elevated inflammatory markers: eliminating the NLRP3 inflammasome in mouse models has been shown to reverse depressive like behaviour and reduce IL-1B levels, which had previously been elevated by stress. There is also a variety of known NLRP3 inhibitors: VX-765 has been shown to decrease levels of IL1β and improve depressive symptoms, and studies focussing on the effect of uncoupling protein 2 also suggest that this regulates the inflammasome.

Preventing overactivation of microglia and astrocytes could also provide a variety of avenues for treatment, given their involvement in neuroinflammation and the pathogenesis of depression. Whilst Minocycline has been proposed as a potential treatment, given its ability to regulate microglia activation and prevent excess inflammation, studies testing whether minocycline has the potential to be a robust treatment for depression have had variable results. Some studies demonstrate that minocycline alleviates depressive symptoms, while other studies suggest that minocycline does not improve depressive symptoms in a generalised population of depressed individuals. The variability of the results could be attributed to the lack of a personalised approach: if immune dysregulation, and consequent inflammation, only causes depression in a subset of patients, then it is likely that preventing microglia activation will only improve symptoms in specific patients.

Conclusion

The Cytokine Hypothesis is only one piece in the complex jigsaw that, when whole, explains the pathogenesis of depression. But testing whether a patient struggling with depression also suffers from a dysregulated immune system could be a useful pointer towards immunotherapy-based approaches, and these immunotherapies have vast potential for further personalisation. Multiple intersecting pathways may be involved in producing an inflammatory response to stress, so targeting these specific pathways, based on which is most likely to be dysregulated in the patient, could be used to prevent the effect that this inflammation has on the neural circuits involved in depression.

Whilst there is indeed light at the end of the tunnel, the pathway to remission is still a complex one. In an ideal world, by personalising patients' treatments, doctors could provide patients with a map and a tailored route to ease the journey towards remission.

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CLINICAL UTILITY OF PHARMACOGENETIC TESTING IN ANTIDEPRESSANT SELECTION: BRIDGING PROMISE AND PRACTICE

By Hossameldin Saber

Finding the Right Antidepressant: Is Genetics the Answer?

Despite advances in antidepressant development and clinician training, approximately 60% of patients fail to achieve symptomatic remission following initial pharmacotherapy for major depressive disorder. (Roberts et al., 2023). This "trial-and-error" approach, requires patients to try an antidepressant for 6-8 weeks, hoping they see a change. If no change is observed, the guessing game continues leading to repeated medication failures. Over time without improvement, physical and cognitive side effects can sabotage future success. Time spent on trialing medications is directly related to financial strain, increase in symptomatology, and nocebo effects. Delays in effective treatment also lead to more patient and physician time spent on trial-and-error, leading to financial strain due to changes in prescription and stigma reinforcement.

But what if a simple genetic test could help avoid all of this?

Pharmacogenetic (PGx) testing, a tool that analyzes your DNA to predict how your body processes medications. PGx testing will predict effectiveness, safety and moreover save time for both physician and patient.

The idea is exciting, like a roadmap for personalized treatment, but not everyone's convinced it works. Some studies say it's groundbreaking; others call it overhyped. In this article, we will break down the latest science, explore why experts disagree, and ask:

Could PGx testing be the key to matching patients with their ideal antidepressant?

The Science Behind PGx Testing: CYP Enzymes and Beyond.

Imagine your body has tiny workers called CYP enzymes (like CYP2D6 and CYP2C19) that metabolize 85% of antidepressants—think of them as your liver's cleanup crew. But here's the catch: your genes determine how fast these workers operate (CADTH Horizon Scan, 2023).

Genetic differences (polymorphisms) in these enzymes classify patients as poor, intermediate, normal, or ultrarapid metabolizers, influencing drug efficacy and adverse drug reactions.

For example:

- Slow workers (poor metabolizers): If your liver enzymes are slow to process certain compounds, such as CYP2D6 and amitriptyline (tricyclic antidepressant), drugs can build up in your system. The more time the antidepressant stays in your body, the more that can lead to unpleasant side effects like dizziness or nausea (Lorvellec et al., 2024).
- Hyperactive workers (ultrarapid metabolizers): If your liver enzymes work too fast as in CYP2C19 enzyme with escitalopram (SSRI antidepressant), drug might get cleared from your body before they produce the targeted effect and lead to underdose and treatment failure (Oslin et al., 2022).

Mixed Evidence from Clinical Trials

Recent large-scale randomized controlled trials (RCTs) present conflicting results:

1. **The GUIDED Study (2019):** Over 1,100 adults living with major depression completed PGx tests to guide antidepressant choice. While genetic-guided treatment didn't dramatically improve depression scores overall, 15% of people using it felt fully better, compared to 10% without it (Greden et al., 2019).
2. **PRIME CARE (2022):** Nearly 2,000 participants diagnosed with major depression completed PGx testing to guide pharmaceutical intervention . PGx testing reduced prescriptions with drug-gene interactions. However, no significant remission difference at 24 weeks (Oslin et al., 2022).
3. **Case Series (2024):** 40 people followed in a case series were diagnosed with either major depression, post-traumatic stress disorder, general anxiety, or bipolar disorder. PGx recommendations were followed in 92.7% of cases, and showed a significantly lower rate of adverse drug reactions and physician assessment of efficacy improved in 79.5% of people (Lorvellec et al., 2024).

A small win, but not a slam dunk.

So, does genetic testing work? It depends on who you ask. Some studies hint it speeds up recovery, others say it's just safer. The debate is still brewing! In my opinion, while the statistical power of these results are not strong, the number of lives impacted provides support that there are cases where it is a clear benefit.

Conclusion

PGx testing represents a paradigm shift toward precision psychiatry, offering tangible benefits in safety and adherence. While RCTs yield mixed efficacy results, real-world data suggest its value could improve the quality of life and reduce clinical burden for healthcare systems (Lorvellec et al., 2024).

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GLOBAL HEALTH AND BEYOND

A REVOLUTION ROOTED IN HISTORY AND A FUTURE FRAUGHT WITH ETHICAL QUESTIONS: PERSONALIZED MEDICINE AS THE NEW LANGUAGE OF PEACE?

by Aliaa Gamal

Imagine standing in an ancient apothecary, where remedies are tailored to each patient based on their symptoms, lifestyle, and environment. Fast-forward to the modern clinic, where a cancer patient's genetic makeup determines the chemotherapy best suited for them. Though separated by millennia, these practices share a fundamental principle: healthcare is most effective when it recognizes individual uniqueness. This is the essence of personalized medicine—an ancient idea reborn through technological innovation. However, alongside its remarkable promise lie ethical dilemmas that challenge their implementation in today's healthcare landscape. Furthermore, as medicine becomes more personalized, it also has the potential to reshape global peace and sustainability, offering a new paradigm where health is a bridge rather than a barrier between nations.

Historical Foundations: Ancient Practices of Personalized Care

Personalized medicine is not as novel as it seems. Ancient healing systems were deeply rooted in the concept of individualized care. Ayurveda, an ancient Indian medical system, classified patients based on their doshas—three biological energies thought to govern physical and mental processes [1]. Ayurveda crafted unique treatment plans, considering the person's constitution, habits, and even seasonal factors. Similarly, Traditional Chinese Medicine (TCM) relied on detailed patient evaluations, such as pulse diagnosis, to identify imbalances in qi, the body's vital energy [2]. The Greek physician Hippocrates, often regarded as the father of medicine, emphasized tailoring treatments to patients' temperaments and environmental influences [3].

However, as medicine transitioned from art to science during the 18th and 19th centuries, the focus shifted toward standardization. The advent of germ theory and mass-produced antibiotics marked a shift to "one-size-fits-all" approaches, where the primary goal was scalability. This uniformity saved millions of lives but often ignored individual variations that could influence treatment outcomes [4].

Today advances in molecular biology, genomics, and artificial intelligence have rekindled the ancient ideal of personalized care, giving it a new scientific foundation.

The Technological Revolution: From Genome to Precision

The Human Genome Project's completion in 2003 marked a significant milestone for modern personalized medicine. For the first time, scientists had a complete blueprint of human DNA, unlocking the potential to study the genetic factors underlying health and disease [5]. This milestone birthed the field of pharmacogenomics, which studies how genetic differences affect drug responses. For instance, genetic testing can tell if a person with breast cancer will benefit from targeted treatments like trastuzumab (Herceptin), which is made for people with HER2-positive tumors [6].

The role of big data and artificial intelligence (AI) has further accelerated this revolution. Wearable devices, such as smartwatches, continuously monitor vital signs, allowing doctors to tailor interventions in real time [7]. AI algorithms analyze vast datasets to identify subtle patterns, enabling predictive and preventive care. For example, AI can flag early signs of heart disease based on a patient's electronic health records and genetic profile [8].

Although the technological advancements are groundbreaking, we must not overlook how they amplify disparities and raise ethical dilemmas.

Ethical Challenges and Global Implications for Peace

The resurgence of personalized medicine brings ethical questions that echo challenges faced in the past while introducing unprecedented complexities. Three key ethical issues stand out: equity and access, genetic privacy, and the societal implications of genome editing. If unaddressed, these challenges risk exacerbating global disparities, but if handled responsibly, they present an opportunity to foster international collaboration and peace.

Equity and Access: A Pathway to Global Stability

One of the most significant challenges is ensuring that personalized medicine benefits everyone, not just the wealthy. Advanced genetic testing and tailored treatments are often prohibitively expensive. For instance, CAR-T cell therapy, a groundbreaking cancer treatment, costs upwards of $373,000 per patient in the United States [9]. These costs place cutting-edge therapies out of reach for most of the global population, particularly in low-income countries.

Financial barriers are not the only source of health inequities. Many genetic studies are disproportionately based on populations of European ancestry, leading to a lack of data on genetic variations in underrepresented groups [10]. These bias risks leave marginalized communities behind as precision medicine advances. If not addressed, this divide could fuel global tensions, with wealthier nations monopolizing life-saving innovations while others remain vulnerable to preventable diseases.

To bridge this gap, initiatives such as a Universal Healthcare Genome Treaty could be established under the United Nations, mandating that all nations contribute to a shared genetic database that benefits humanity. Countries would be required to allocate a percentage of their biotech advancements to humanitarian efforts, ensuring that personalized medicine does not become a privilege but a universal right.

Genetic Privacy, Data Sovereignty, and Diplomacy

Personalized medicine relies heavily on genetic data, raising concerns about privacy and consent. Direct-to-consumer genetic testing companies, such as 23andMe, collect vast amounts of data from individuals, often sharing this information with third-party researchers or pharmaceutical companies [11]. While these collaborations can accelerate medical breakthroughs, they also expose individuals to risks such as genetic discrimination.

The Genetic Information Nondiscrimination Act (GINA) in the United States provides some protection, prohibiting discrimination by health insurers and employers based on genetic data [12]. However, the law does not extend to other areas, such as life insurance or long-term care insurance. This legal gap leaves many individuals hesitant to participate in genetic testing or research studies.

This issue extends beyond individuals to entire nations. If one country dominates the collection and analysis of genetic data, it could wield unprecedented power in biopolitics. Governments could use genetic insights for national security, economic advantage, or even bioengineering superior traits in their populations. Establishing global standards for genetic data sovereignty and ethical research collaborations could prevent genetic information from becoming a tool of division rather than unity.

The Future of Personalized Medicine: A Double-Edged Sword

As personalized medicine continues to evolve, its future is filled with both promise and peril. On one hand, it has the potential to revolutionize healthcare by making treatments more effective and minimizing trial-and-error approaches. AI-driven tools could democratize access to care by enabling early disease detection and remote monitoring, particularly in underserved areas [13].

On the other hand, the rapid pace of innovation threatens to outpace the development of ethical and regulatory frameworks. For example, who owns the data generated by wearable devices or large-scale genomic studies—the individual, the healthcare provider, or the company? Without clear policies, data misuse could undermine public trust in personalized medicine.

The vision of equitable personalized medicine can only be realized if stakeholders—scientists, clinicians, policymakers, and patients—work together to address these challenges. Initiatives like the All of Us Research Program, which aims to build a diverse health database, represent steps in the right direction [14]. However, we must do much more to match innovation with inclusivity and accountability.

Conclusion: Personalized Medicine as a Force for Global Peace and Sustainability

Personalized medicine represents a convergence of ancient wisdom and modern science, offering a glimpse into a future where healthcare is tailored to the unique needs of every individual. However, its potential to transform lives must be tempered by a commitment to equity, privacy, and ethical responsibility.

More than just a medical revolution, personalized medicine has the potential to be a diplomatic tool for peace and sustainability. Stakeholders can help make sure that personalized medicine lives up to its promises without breaking them by fighting for fair access, upholding ethical standards, and adopting a patient-centered approach. In the end, the true measure of success will not be the technology itself but the humanity with which it is applied. In a world where healthcare is accessible, ethical, and sustainable, peace is not just an ideal but a reality.

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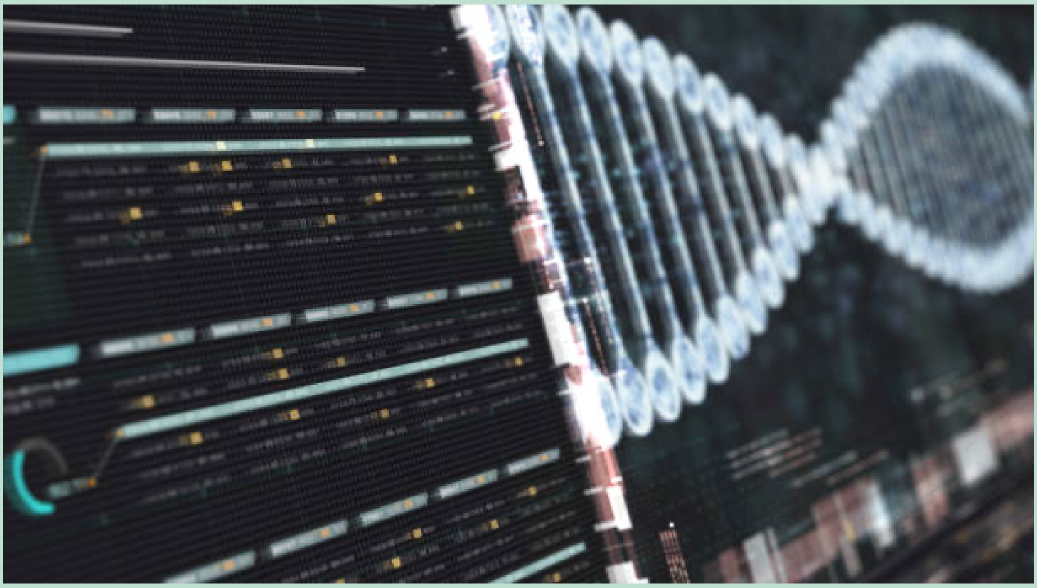
Translational Bioinformatics and Its Role in Personalised Medicine

by Vivien Karen Mok



Introduction

Technological innovations advances over time, among these, the promise of personalised healthcare. Fields like translational bioinformatics unravel the complexities of human health – attributed to innumerable factors ranging from sex, lifestyle, genetics, and environment, and develop machine learning models to predict prevalence to disease and tailor solutions.

My favourite modules this semester were translational biomedicine and bioinformatics. While it may seem unusual to have a "favourite", I found the novel interplay between these two fields for clinical application highly intriguing. Translational biomedicine is the field focused on translating laboratory research findings into clinical trials to initiate practical clinical applications. Bioinformatics is the field whereby computational tools and softwares are used to store, retrieve, and analyse large amounts of biological data. With the growing abundance of data, translational bioinformatics (TBI) emerges as a field that combines translational biomedicine and bioinformatics, leveraging computational information systems derived from pivotal biomedical research to improve public health outcomes.

One clinical trial study that stood out and prompted me to write about this topic is by Nielson et al. (2020), titled "Data integration for prediction of weight loss in randomized controlled dietary trials".

The main objective of this study is to collect various anthropometric and physiological data of a Danish population that undergoes different diet types, to be inputted into a machine learning algorithm for optimising weight loss prediction and personalise dietary plans. Advanced bioinformatics tools and techniques were used to analyse the host genome and gut microbiome of each participant. Hence, enabling their integration into a random forest algorithm, a machine learning model based on decision trees, which predicts both an individual's likelihood of achieving weight loss with a specific diet and the potential amount of weight they might lose by analysing their biological data. This paper effectively demonstrates how TBI can be applied to advance personalised medicine, hence convincing me to showcase its potential to tailor healthcare solutions to individuals with unique biological profiles.

Subtyping/classification of omics

Following the completion of the Human Genome Project, there has been exponential increase of development and generation of large datasets in the multi-omics (eg. genomics, proteomics). "-omics" refers to the scientific study (quantifying, analysing etc.) of an entire set of biomolecules, for example, genomics – the study of an organism's entire genome (1). Some randomised controlled trials used in translational biomedicine, rely on multi-omics data collection – like Nielson et al (2020). By identifying and categorising each sample into subtypes and classifications, multi-omics data serves as a foundation for actionable research.

The translation of these multi-omic datasets to practical applications is the pivotal step to developing a solution for practical implementation of research knowledge in clinical settings. With the rise in AI-based technology, there has been significant growth in integrating multi-omic data to develop predictive models. How are the samples from the trials identified and categorized? This is where computational bioinformatics tools play a crucial role. These tools enable the efficient retrieval and analysis of large datasets, such as genome sequences, by using platforms like genome browsers (eg. UCSC Genome Browser). They compare trial samples against reference datasets and extract the relevant sections needed to feed into machine learning algorithms (eg. Scikit-learn or TensorFlow) for further analysis and pattern recognition.

Case studies

Computational bioinformatics tools have paved the way for handling the large volume and complexity of genomic data, enabling groundbreaking research and innovation—particularly in personalised medicine (3). A notable example is The Cancer Genome Atlas (TCGA) project, which analyzed the genomes of diverse cancer samples to identify genetic mutations associated with specific cancer types (4). Using advanced bioinformatics tools, TCGA facilitated the development of targeted therapies, allowing for precise and effective treatment strategies tailored to individual patients. Beyond these achievements, TCGA has provided a vast repository of publicly available data, empowering scientists worldwide to build upon its findings and drive further advancements in cancer research and treatment. The project also continues to refine bioinformatics tools, enabling more detailed analyses and fostering new discoveries. Recently, TCGA has expanded into machine learning algorithms, leveraging these powerful tools to improve diagnostic accuracy and develop even more effective predictive models.

Ethics

Carrying out a large-scale operation involving extensive datasets requires meticulous planning and ethical considerations. In the context of multi-omics studies, which encompass a wide range of anthropometric and physiological measurements – including sensitive biological data like genomes, it is imperative to ensure that participants are fully informed about the nature of the data being collected, as well as its storage and intended use. The data collected should also be stored in a secure platform with robust measures to prevent unauthorised access. Additionally, blinded randomised trials should work best to prevent researcher's bias. All these mentioned factors are especially relevant to TBI as it involves processing large amounts of data through many different application platforms. Considering these factors to safeguard data privacy and confidentiality, crucial for adhering to just principles (6).

Conclusion

The impact of TBI on the field of personalised medicine within oncology and rare diseases have already shown great outlook, representing the vast potential for expanding and developing TBI for other specialities. Through this expansion, machine learning algorithms are able to refine prediction accuracy with varying populations. If executed conscientiously, use of predictive technology can improve public health and safety through personalised treatments. Unlocking the full potential of personalised medicine requires substantial investments in TBI research and infrastructure. As evidenced, the great potential of TBI lies in advancing medical science and transforming patient care, ultimately redefining the boundaries of possibilities in modern healthcare.

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CRISPR TECHNOLOGY: AN ATTEMPT TO CONTROL THE FUTURE? WHOSE FUTURE?

by Efrain Uh

The Transformative Power of CRISPR Technology

Over the past few decades, scientific progress has moved from simply decoding the genetic language of life to actively rewriting the rules of inheritance. Advances in CRISPR-based (Clustered Regularly Interspaced Short Palindromic Repeats) technologies, synthetic biology, and computational modeling have enabled an unprecedented level of precision in modifying genetic material - capabilities that were once confined to the realm of science fiction.

CRISPR particularly represents a groundbreaking gene-editing tool. Functioning as a highly accurate genetic "cut-and-paste" system, CRISPR particularly employs the Cas9 enzyme (Figure 1) to locate and excise specific DNA sequences (Koonin and Makarova, 2019). These sequences can then be removed or replaced with alternatives that correct genetic errors or introduce desired traits, enabling targeted genetic modifications with remarkable speed, accuracy, and efficiency. Notably, CRISPR's origins trace back to microbiological research into the immune defenses of bacteria used in yogurt production. What began as a niche scientific inquiry has since evolved into a powerful platform with wide-ranging applications in biomedicine, agriculture, and public health.

Today, scientists can harness CRISPR to precisely insert beneficial genes or eliminate harmful ones, offering promising therapeutic avenues for genetic disorders, infectious diseases, and other pressing health challenges. As this technology rapidly advances, it presents both extraordinary opportunities and complex ethical and policy considerations (*Figure 2*) that must be addressed to ensure equitable and responsible implementation.

Therapeutic Promise and the Risk of Reinforcing Social Inequities

CRIPS-based technologies hold transformative potential for somatic gene editing, particularly in the treatment of severe and previously untreatable human diseases. CRISPR may enable therapeutic interventions for more than 7,000 known genetic disorders (Baer, 2024), offering new hope for patients and families affected by rare and debilitating conditions. One notable example is the application of CRISPR to correct the genetic mutations underlying sickle cell disease, a breakthrough that exemplifies the broader promise of gene-editing tools in precision medicine. Beyond direct clinical applications, CRISPR also provides a powerful platform for advancing genomic research. Its precision and adaptability are accelerating discoveries related to gene function, regulation, and interaction, deepening our understanding and appreciation of the human genome.

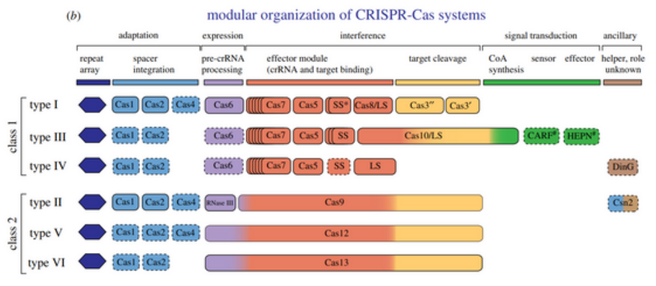
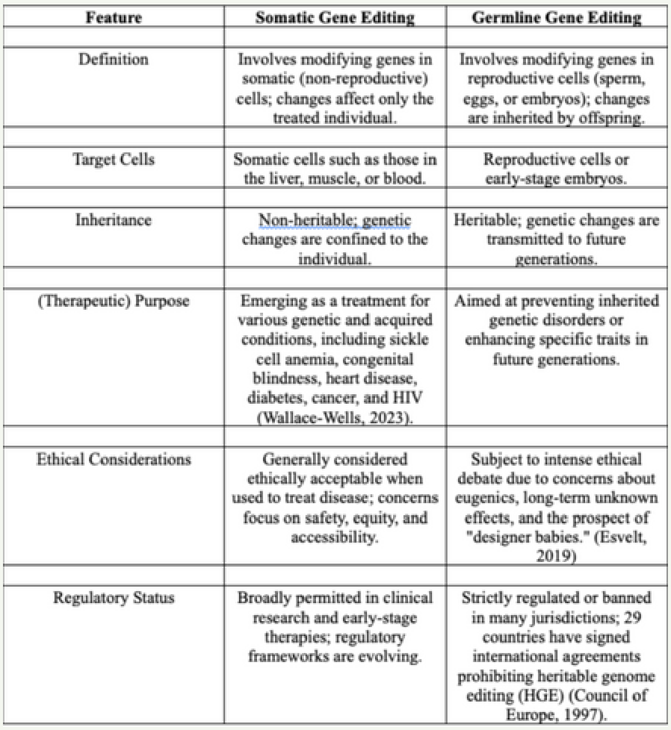


Figure 1. Class I and Class II (Modular Organization Of) CRISPR-Cas Systems (Koonin and Makarova, 2019)

Figure 2. CRISPR: From Scientific knowledge → Technological Applications → Socio-ethical Implications

However, these advances are accompanied by significant ethical and societal risks - particularly in the context of germline editing. Unlike somatic interventions, germline modifications are heritable and may permanently alter the human gene pool (Table 1: *Somatic vs. Germline gene editing*).



Feature	Somatic Gene Editing	Germline Gene Editing
Definition	Involves modifying genes in somatic (non-reproductive) cells; changes affect only the treated individual.	Involves modifying genes in reproductive cells (sperm, eggs, or embryos); changes are inherited by offspring.
Target Cells	Somatic cells such as those in the liver, muscle, or blood.	Reproductive cells or early-stage embryos.
Inheritance	Non-heritable; genetic changes are confined to the individual.	Heritable; genetic changes are transmitted to future generations.
(Therapeutic) Purpose	Emerging as a treatment for various genetic and acquired conditions, including sickle cell anemia, congenital blindness, heart disease, diabetes, cancer, and HIV (Wallace-Wells, 2023).	Aimed at preventing inherited genetic disorders or enhancing specific traits in future generations.
Ethical Considerations	Generally considered ethically acceptable when used to treat disease; concerns focus on safety, equity, and accessibility.	Subject to intense ethical debate due to concerns about eugenics, long-term unknown effects, and the prospect of "designer babies." (Esvelt, 2019)
Regulatory Status	Broadly permitted in clinical research and early-stage therapies; regulatory frameworks are evolving.	Strictly regulated or banned in many jurisdictions; 29 countries have signed international agreements prohibiting heritable genome editing (HGE) (Council of Europe, 1997).

Of particular concern is the potential for germline enhancement to exacerbate existing social inequalities and inequities. Access to such technologies may be disproportionately available to the wealthy and powerful, enabling them to confer genetic advantages to their offspring and further entrenching systemic disparities (Baylis and de Vries, 2021). Heritable genome editing (HGE) – a subset of germline gene editing - like many cutting-edge biotechnologies, is costly and complex - characteristics that risk reinforcing existing social hierarchies. Without deliberate policy intervention, its deployment may exacerbate social and economic disparities by increasing access for the privileged while marginalizing underserved populations.

To address these risks, it is imperative that clinical trials, research priorities, and funding mechanisms focus on the equitable application of CRISPR and related technologies. Investments should prioritize therapies that offer the greatest benefit to historically underserved communities - nationally, regionally, and globally.

Balancing Promise and Peril: the Ethical Tension in Heritable Genome Editing (HGE)

Critics argue that the pursuit of HGE may be driven less by therapeutic necessity and more by the desire to enhance human traits. Regalado (2015) suggests that the ambition to augment future individuals' capacities may be the underlying motivation for much of the interest in HGE - particularly given the comparatively weak therapeutic justification for altering the germline (Darnovsky and Hasson, 2020).

In fact, proponents of genetic enhancement have begun cataloging so-called “protective gene variants” that could be used to give future children a biological advantage. These include genes associated with increased bone density, leaner muscle composition, reduced pain sensitivity, and even lower body odor (Knoepfler, 2015). Such efforts raise significant concerns about equity, consent, and the long-term effects of altering the human genome - effects that may not become apparent until generations later.

Ethical Risks of Germline Enhancement: A Critical Perspective

In fact, bioethicist Rosemarie Garland-Thomson (2024) warns that germline gene editing for human enhancement could result in morally unacceptable outcomes, including unintended medical harms and the erosion of meaningful informed consent. Furthermore, germline enhancement risks exacerbating genetic discrimination and deepening existing social inequalities. It may foster a culture of conditional parental acceptance - where children are valued based on their engineered traits - thus undermining the inherent dignity and diversity of human life. Garland-Thomson also cautions against the commodification of human beings, as gene editing technologies become entangled with market incentives and the expansion of a profit-driven biomedical industry. Finally, the normalization of enhancement-oriented interventions could legitimize unregulated or unethical scientific practices, posing long-term risks to public trust and global health governance. So, are we truly ready to take on the responsibility of building a (more equitable) future that has never existed before?

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Healing Divides: Personalised Medicine as a Catalyst for Global Peace

By Mazhar Elshorbagi and Yasmin Hamdy

Amidst a time marked by intricate geopolitical conflicts and the collective recollection of a worldwide pandemic that highlighted our deep interconnections, the quest for creative routes to peace and security has become increasingly pressing. Beyond the conventional domains of diplomacy and trade agreements, a new area is emerging at the crossroads of healthcare and global affairs: Personalized Medicine Diplomacy (PMD). This emerging discipline reshapes the function of medical science, not merely as a means to treat illness, but as a powerful driver for establishing trust, reducing entrenched health disparities, and ultimately nurturing a more harmonious global society. Utilizing the groundbreaking possibilities of therapies customized to a person's distinct genetic profile, lifestyle, and surroundings, PMD presents a unique type of soft power based on a common aspiration for a healthier future for all people. The path to personalized medicine started in earnest with the conclusion of the Human Genome Project, a significant global research initiative that charted the full human DNA. This accomplishment, documented in publications such as Science, did more than reveal the mysteries of our genetic code; it established the foundation for a new framework in healthcare (Science, 2001). For the first time, it became possible to move beyond a "one-size-fits-all" approach to medicine and envision treatments designed for the individual. The applications are vast and transformative, from mutation-specific therapies for cystic fibrosis to advanced immunotherapies that prime a patient’s immune system to fight cancer. As research published in Nature has explored, new technologies like prime editing are pushing the boundaries even further, offering the potential to correct the vast majority of known pathogenic genetic variants, heralding a new era of precision in medical science (Nature, 2019).

The Intersection of Health and Peace

Health and peace are deeply interconnected. The WHO’s *Global Health and Peace Initiative (GHPI)* highlights that 80% of the WHO’s humanitarian caseload and 70% of disease outbreaks occur in fragile and conflict-affected settings. Armed conflicts disrupt healthcare systems, exacerbate inequalities, and fuel grievances. Personalized medicine, by addressing individual and community-specific health needs, can mitigate these tensions and serve as a diplomatic tool for reconciliation.

Personalized Medicine Diplomacy (PMD): A New Framework

PMD acknowledges that fair access to customized therapies can build trust between countries, decrease health inequalities, and encourage stability. The UN's Thematic Paper on Health and Peace highlights that limited access to healthcare intensifies conflicts, whereas inclusive health policies can provide neutral spaces for dialogue. PMD utilizes this principle by promoting international partnerships in genomic studies, fair medication distribution, and culturally aware healthcare policies.

This medical breakthrough establishes the groundwork for PMD, a principle that strategically incorporates these cutting-edge health technologies into international relations. It represents an advancement in health diplomacy, recognized for a long time as a way to attain two objectives: enhancing global health and bolstering international ties. A National Defense University report emphasized that medical diplomacy can foster substantial goodwill and offer distinctive access to key decision-makers, acting as an influential tool and a way to mend diplomatic shortcomings, especially in areas prone to conflict. PMD advances this concept by emphasizing the collaborative, data-rich aspect of personalized medicine as the key method for creating connections. The complex task of creating and providing tailored therapies requires extensive global collaboration, including the exchange of genomic information and the joint development of regulatory structures.

The core of PMD's potential lies in its ability to cultivate trust through collaborative science. The success of personalized medicine on a global scale is contingent upon the secure and ethical sharing of vast amounts of genomic and health data from diverse populations. As the "Human Variome Project" outlined in *Science & Diplomacy*, the goal of collecting and understanding all human genetic variation can only be achieved through a coordinated, global effort. This level of data sharing, however, is impossible without a strong foundation of trust—trust between individuals and researchers, and, crucially, between nations. A global survey by the Global Alliance for Genomics and Health (GA4GH) found that while personal doctors are highly trusted with genomic data, trust in international and commercial entities is significantly lower, underscoring the challenge. PMD addresses this by creating frameworks for collaboration that are built on transparency, mutual benefit, and shared governance.

International partnerships, such as the cross-border health information systems and collaborative projects on chronic diseases led by organizations like the Taiwan ICDF, demonstrate a model for this in action. When nations work together to tackle a shared health challenge—be it a specific cancer that affects their populations or a rare genetic disorder—they are compelled to establish common protocols, ethical guidelines, and data security standards. This process of co-creation fosters a sense of shared ownership and mutual respect. The World Health Organization's (WHO) Science Council, in its 2022 report, Accelerating access to genomics for global health, strongly advocates for such collaborative models, emphasizing that pooling resources and expertise, particularly through regional programs, is essential for building technical capacity and ensuring equitable access. These scientific partnerships can create powerful, positive spillover effects, building channels of communication and understanding that can withstand and even help mitigate political disagreements.

Case Studies: Personalized Medicine as a Peacebuilding Tool

In spite of these difficulties, various worldwide initiatives demonstrate how personalized medicine contributes to promoting peace:

- Middle East Genomic Partnership: Despite political conflicts, nations in the Middle East have participated in cooperative genomic studies to tackle hereditary illnesses common in the area. This collaboration in science has enhanced diplomatic relationships and encouraged shared understanding.

- African Union’s Precision Health Initiative: By incorporating personalized medicine into public health approaches, African countries have enhanced healthcare equity, diminishing ethnic and regional inequalities that frequently lead to social unrest.
- European Union Personalized Medicine Framework: The EU has implemented cross-border healthcare arrangements with fair access to tailored therapies, strengthening unity among member nations.

Furthermore, PMD is critical in addressing one of the most persistent and destabilizing forces in our world: global health disparity. The stark reality is that the benefits of medical advances are not shared equally. A paper in *Functional & Integrative Genomics* notes that underrepresented populations and those in low- and middle-income countries (LMICs) face systemic barriers leading to significant health inequities. There is a legitimate fear that personalized medicine, with its sophisticated infrastructure requirements and high costs, could exacerbate these divides, creating a world of "genomic haves and have-nots." A publication in *The Lancet* on health equity in precision medicine highlighted this very risk, questioning whether the genomics revolution will ameliorate or widen the gaps in healthcare access and outcomes (The Lancet, 2023).

PMD offers a direct response to this challenge by reframing the global rollout of personalized medicine not as a market-driven competition but as a collective responsibility. This involves high-income nations and international bodies actively assisting LMICs in building the necessary capacity. The WHO’s 2022 report outlines a clear roadmap for this, calling for tiered pricing models, the sharing of intellectual property for low-cost versions of technologies, and robust investment in knowledge transfer and laboratory infrastructure in LMICs. By assisting in the creation of local and regional centers for genomic research and clinical care, PMD can enable countries to meet the particular health demands of their own citizens, not only enhancing health results but also reinforcing national health systems, boosting pandemic readiness, and cultivating a sense of worldwide unity. It is a concrete indication that the well-being of one country is fundamentally connected to the well-being of all.

Despite that, the path to a reality where personalized medicine acts as a common driver of peace encounters significant obstacles. The challenges are considerable, comprising the major financial barriers of these advanced treatments, the profound ethical and legal concerns tied to data privacy, and the pronounced global disparities in infrastructure and expertise. The threat of "genomic nationalism" exists, as countries gather important data, viewing it as a strategic asset rather than a shared global resource. Tackling these issues requires a cohesive and continuous worldwide effort, guided by the principles of PMD.

The way forward necessitates the development of robust global governance frameworks for genomic data, ensuring that sharing is secure, ethical, and equitable. Creative partnerships between the public and private sectors are crucial for cutting costs and improving access to these vital therapies. It demands a global commitment to open science, where data and research findings are shared widely to accelerate discoveries for the benefit of all. Ultimately, it encourages continuous investment in capacity-building projects that allow scientists, clinicians, and policymakers worldwide to participate in and promote the personalized medicine shift.

In conclusion, PMD provides an innovative outlook for the 21st century. It is a framework that acknowledges the deep human yearning for a healthy existence as a foundation for establishing connections of trust and collaboration. By integrating the values of equity, teamwork, and mutual respect into the core of our development and implementation of cutting-edge medical science, we can achieve more than merely healing individual bodies. We can begin to heal the fractures that divide our world. Personalized medicine holds the potential not only to grant longer, healthier lives but to serve as a powerful, enduring catalyst for global peace, proving that the most sophisticated science, when guided by a deep sense of shared humanity, can be our most effective diplomatic tool. As the world navigates complex geopolitical challenges, Personalized Medicine Diplomacy offers a pathway toward a more inclusive and peaceful future.

Mapping Pathways of Embodiment Using Precision Medicine

By Nandini Kapoor

Introduction - Defining Epigenetics

Genes are often thought of as the blueprint for physiological processes. These fundamental units of heredity are passed from parents to their children, containing the information that determines our physical traits and characteristics. Until fairly recently, genes were viewed as immutable, fixed entities. But what if our surrounding environment can influence how our genes function?

This phenomenon is known as epigenetics: the study of how environmental factors modify gene expression without altering the underlying DNA sequence1. Perhaps the blueprint remains the same, but the builder may adjust the construction of the house based on available resources. Similarly, environmental inputs can determine which genes are turned on or off. These epigenetic modifications reveal that gene expression is dynamic and responsive to external stimuli, enabling our bodies to adapt to unique social and physical contexts.

Social Determinants of Health Are Embodied

Other than epigenetics, attention has also grown around social determinants of health: The conditions in which people are born, live, work, and age, which profoundly shape their health outcomes. These determinants are embedded within social structures and institutional forces that distribute resources, power, and opportunity unequally. Discriminatory systems, including racism, casteism, and classism, produce health inequities by limiting access to safe housing, quality education, clean environments, and healthcare.

Ecosocial theory posits that these social and material conditions are embodied, or literally biologically incorporated. Daily exposure to adverse environments can "get under the skin," influencing not only psychological well-being but also physiological outcomes2. Over time socioeconomic disadvantage manifests in the weathering hypothesis: chronic stress leads to the premature decline of the body's normal functions 3.

Social Epigenetics

This raises a critical question: how do we measure the biological embedding of social experience? Social epigenetics is an emerging subfield of precision medicine that seeks to answer this question. It investigates how social environments can lead to molecular-level changes in gene expression, increasing susceptibility to disease. This field links macrosocial forces, such as structural inequality or historical trauma, to micro-level biological outcomes4.

For example, exposure to pollutants in marginalized neighborhoods has been shown to trigger pro-inflammatory gene expression, heightening the risk of cancer and respiratory illnesses5. Likewise, experiencing chronic discrimination elevates cortisol, a stress hormone that can dysregulate immune function and increase vulnerability to illness6. These are molecular imprints of inequality.

Case Study: The Intergenerational Impact of British Colonialism and Caste-Based Discrimination on Health Outcomes

Social epigenetics provides a lens through which to examine the long-term and intergenerational health impacts of colonialism and caste-based discrimination. Low birth weight and child stunting are both significant public health concerns in India, which have lifelong health consequences[7,8]. They are not merely the result of individual behaviors, but are shaped by historical legacies and systemic inequality.

The caste system in India, originally stratified by occupation, created rigid social hierarchies. At the top were the Brahmins (priests), followed by the Kshatriyas (warriors), Vaishyas (merchants), and Shudras (laborers), with the Dalits (street sweepers) at the bottom. Under British colonial rule, caste divisions were codified and intensified through policies such as segregated schools[9]. During World War II, the colonial administration reversed earlier labor protections, compelling lower-caste women to work in hazardous coal mines to meet fuel demands. Concurrently, the Bengal Famine, which was exacerbated by wartime policies, led to widespread malnutrition, particularly among lower-caste individuals[10]. The impact of the famine and toxins from the coal mines extended beyond immediate loss of life. It created metabolic disruptions and epigenetic changes that increased risks for low birth weight and stunting in subsequent generations: a stark example of how historical injustices can be biologically inherited[11].

Although caste discrimination was officially outlawed in 1950, its structural impacts persist, and many caste-based norms continue to be internalized and persist across generations. Caste-based inequities in access to health-promoting resources continue to perpetuate these adverse birth outcomes, reinforcing a cycle of disadvantage[9].

The Potential of Social Epigenetics

Social epigenetics offers a framework to map these biological consequences of structural violence. By identifying the molecular pathways of environmental etiology of disease, it offers compelling evidence about the role of structural discrimination in impacting health outcomes[4]. This can strengthen calls for policy change by demonstrating that social inequities leave measurable biological scars. Furthermore, identifying molecular signatures of disease can help inform the allocation of resources: which social programs will most appropriately support marginalized populations? These findings can direct interventions to interrupt the intergenerational cycle of disadvantage from becoming biologically embedded. Hence, rather than focusing solely on genetic differences, a socially attuned model of precision medicine incorporates context – history, environment, and lived experience – into both diagnosis and treatment.

Potential Ethical Concerns

While social epigenetics offers powerful insights into the mechanisms linking inequality to health, it also raises significant ethical concerns. One major risk is biological essentialism, which is the misinterpretation that marginalized communities are biologically inferior or inherently diseased, rather than shaped by their environments. Without careful framing, epigenetic findings may inadvertently reinforce stigma or shift responsibility for health outcomes away from societal structures and onto individuals.

Additionally, questions arise regarding consent, privacy, and data ownership, especially when collecting sensitive biological data from historically marginalized communities. Who controls this data, and how is it used? There is a moral imperative to ensure that research does not exploit vulnerable populations under the guise of scientific progress[12].

Implications of Integrating Precision Medicine

Integrating precision medicine with insights from social epigenetics holds transformative potential, but only if done with equity at its core. Precision medicine traditionally aims to tailor treatment based on individual genetic profiles, but when combined with an understanding of social context, it can move beyond individualized care to address structural determinants of health.

A socially-informed precision medicine approach would advocate not only for targeted therapies but also for upstream interventions: reducing exposure to environmental toxins, combatting discrimination, and promoting policies that address food insecurity and housing inequality. In doing so, it reframes medicine not just as a tool for treatment, but as a pathway for justice.

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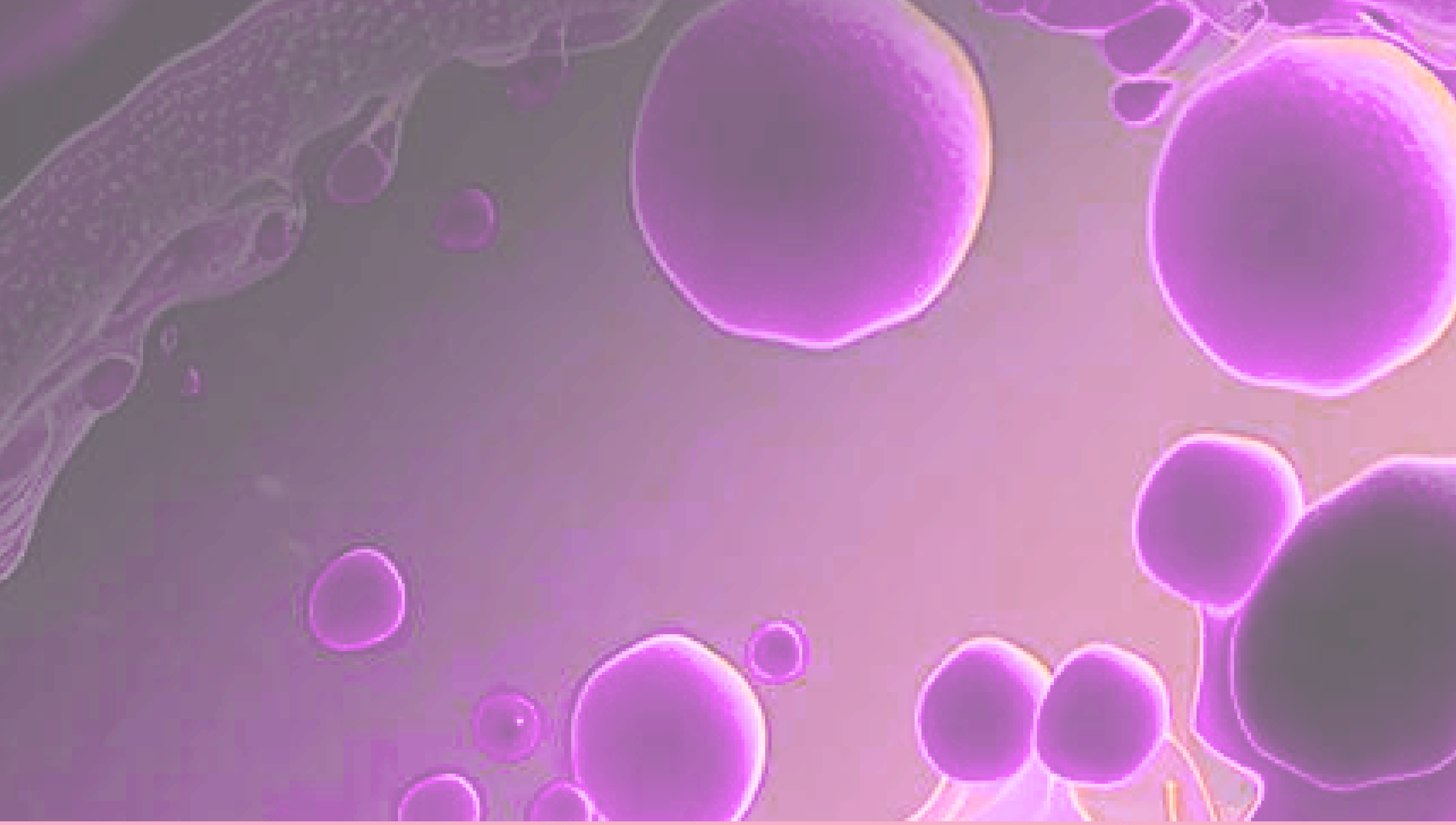
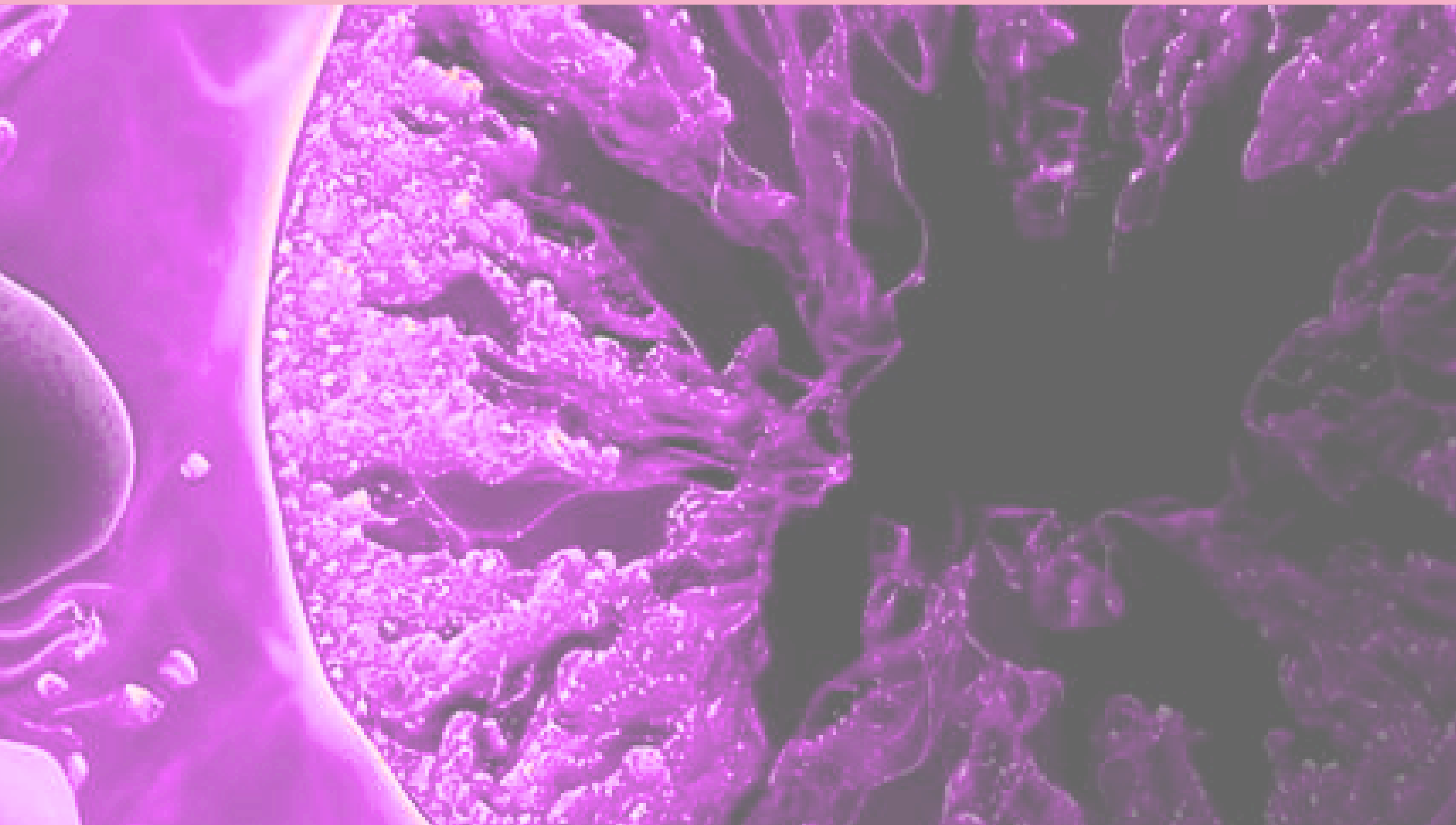


CANCER



Understanding p16: A Key Biomarker for HPV-Positive Head and Neck Cancer

by Zehra Azim

What is HPV-Positive Head and Neck cancer (HCN)?

HCN affects important areas of our body including the mouth, throat, and voice box. It is the sixth most common cancer worldwide, causing 3.6% of all cancer deaths (Chi et al., 2023). While HCN has traditionally been linked to smoking and alcohol use, doctors are seeing a troubling rise in cases caused by the human papillomavirus (HPV) - the same virus that can cause cervical cancer. In some regions, HPV-positive HCN now makes up 38-80% of throat cancer cases and 30% of all HCN cases (Chaturvedi et al., 2013; Zamani et al., 2020). This shift in what is causing this cancer has led doctors to develop new ways of detecting and treating it.

What is p16 and Why Does it Matter?

Think of p16 as a cellular traffic light. In normal cells, it functions as a tumor suppressor protein by inhibiting cyclin-dependent kinases (CDK4/6), which prevents cell cycle progression from G1 to S phase (Romagosa et al., 2011). This regulation helps control cell growth by acting as a "stop" signal, preventing excessive and uncontrolled cell division.

However, when high-risk HPV strains (particularly HPV-16 and HPV-18) infect cells, viral oncoproteins E6 and E7 interfere with normal cell processes. Specifically, E7 binds to the retinoblastoma protein (pRb), causing its inactivation and degradation. This disruption leads to a compensatory dramatic spike in p16 expression through a negative feedback loop (Münger et al., 1989; Wai et al., 2020). This makes p16 an excellent warning sign, or biomarker - when doctors find high levels of p16 in head and neck tumours, it usually means HPV is present. Understanding p16 levels has become crucial in determining the best treatment approach for patients (Fakhry et al., 2018).

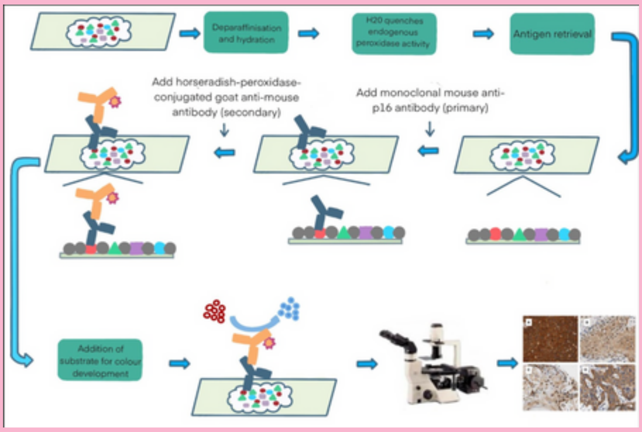


Figure 1 (adapted from Sino Biological and Zhao et al., 2012). A visual representation of p16 immunohistochemistry.

How Does Testing for p16 Work?

Doctors can test for p16 using immunohistochemistry (IHC) (Zhao et al., 2012; Sino Biological, n.d.) (Figure 1). This is like using a special highlighter that makes p16 visible under a microscope. The process involves biopsying a small sample of the tumour and treating it with antibodies that bind to p16, making it show up in bright fluorescent colours. This allows doctors to see if p16 levels are abnormally high. According to guidelines from major medical organisations, this test should show p16 in at least 70% of the cancer cells to be considered positive (Lewis et al., 2018). The test is widely available in medical centres and provides results relatively quickly, making it a practical tool for doctors.

The process begins with deparaffinisation, which removes the paraffin wax used to preserve tissue samples, allowing antibodies to access cellular proteins. Without this crucial step, antibodies would be unable to reach and bind to the p16 protein targets within the tissue. Following deparaffinisation, antigen retrieval is performed to unmask epitopes that may have been altered during tissue fixation. Next, endogenous peroxidase blocking prevents false positive signals from naturally occurring peroxidases in the tissue. The primary antibody specific to p16 is then applied, which binds directly to p16 proteins in the tissue.

A secondary antibody conjugated with horseradish peroxidase (HRP) subsequently binds to the primary antibody. When a chromogen substrate is added, it reacts with HRP to produce a colored precipitate, making p16 proteins visible under a microscope. Finally, counterstaining with hematoxylin provides contrast by colouring cell nuclei blue, allowing pathologists to clearly identify p16-positive cells (brown) against the tissue background.

The Good and the Bad

The p16 test has proven particularly valuable for throat cancer, where it is most accurate and helpful (Schache et al., 2011). It is relatively quick and affordable compared to other testing methods, and it helps doctors predict how well treatment might work. This information is crucial because patients with HPV-related cancer often respond better to treatment than those caused by other factors (Lassen et al., 2009). Typical treatments for HPV-related throat cancer include reduced-intensity radiation therapy, targeted immunotherapies, and in some cases, minimally invasive surgical approaches like transoral robotic surgery (TORS). Understanding p16 levels gives doctors crucial information that helps them make better treatment decisions.

However, the test is not perfect. It can be less reliable in detecting HPV in some areas of the head and neck besides the throat (Lingen et al., 2013). Sometimes results are not completely clear due to issues like off-target antibody binding or variable staining intensity and need additional testing to confirm. Different laboratories might interpret results slightly differently, which can occasionally lead to confusion (El-Naggar and Westra, 2012). These limitations have pushed researchers to look for ways to improve the testing process.

Part of a Bigger Picture

While p16 testing is important, it is just one part of how doctors diagnose and treat HCNs. Sometimes doctors also use other methods like testing for HPV DNA or RNA. Each method has its own strengths: p16 testing is quick and widely available, DNA testing can measure how much virus is present, and RNA testing can show if the virus is actively affecting the cancer cells (Wang et al., 2013).

The cost and availability of these different tests vary significantly. While p16 testing is relatively inexpensive and available in most hospitals, some of the newer testing methods require special equipment and expertise. This means doctors need to carefully consider which tests will be most helpful for each patient while keeping in mind practical concerns like cost and accessibility.

Looking to the Future

Scientists are working on exciting new ways to make p16 testing even more reliable and useful. One promising approach involves using artificial intelligence to help interpret test results more accurately (Gurcan et al., 2009). This could help eliminate some of the variation between different laboratories and make results more consistent.

Another exciting development is the use of machine learning - a type of artificial intelligence - to analyse test results. These computer systems can spot patterns that might be hard for human eyes to see, potentially making diagnosis more accurate. They could also help predict which treatments might work best for each patient, moving us closer to truly personalised cancer care (Tran et al., 2021).

Researchers are developing advanced testing methods that combine p16 with other biological markers such as E6/E7 mRNA, HPV DNA, and cell cycle regulators like Ki-67 (Shi et al., 2009). By looking at multiple signals from cancer cells at the same time, doctors can get a more complete picture of each patient's cancer. This is like having multiple pieces of evidence instead of relying on just one clue.

The Bottom Line

While not perfect, p16 testing has become an essential tool in fighting HCN. It helps doctors identify which cases are caused by HPV and guides them in choosing the most effective treatments. As technology improves and new methods are developed, p16 testing will become even more valuable in helping doctors provide the best possible care for their patients.

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Emerging biomarkers in endometrial cancer and potential application

by Jenusiya Jeyaseelan

In 2023, endometrial cancer surpassed ovarian cancer and became known as the most lethal gynaecologic malignancy. Due to recent advances in our ability to analyse patients and their tumours using combinatorial approaches, endometrial cancer is currently leading in the evolution of precision medicine. However, many technical challenges still persist in these techniques, though the ongoing elucidation of tumour biomarkers shows promise of furthering progress in this field.

Endometrial cancer, also known as uterine cancer, is the fourth most common cancer in women worldwide, affecting 3% of women during their lifetime. It begins as abnormal growth of the cells in the endometrium, which lines the uterus. The primary presenting symptom is abnormal uterine bleeding which occurs in about 90% of cases. Diagnosis is subsequently confirmed through imaging techniques such as: transvaginal ultrasound and further sampling. These diagnostic techniques enable around 80% of women to be diagnosed at an early stage, however, the challenge of detecting disease in asymptomatic patients still remains. This stresses the need for improved screening methods and biomarker development so that we detect the cancer early before it develops into a malignant entity.

Biomarkers are traits that doctors measure in your blood, body fluids, and tissues, indicative of diseases or normal bodily functions. Furthermore, biomarkers can be used to test the effectiveness of treatments for a disease you have. In the case of cancer, biomarkers include proteins, genes, or other substances in your body. The most extensively studied blood-based biomarkers of endometrial cancer are cancer antigen 125 (CA-125) and human Epididymis protein 4 (HE4). Despite their potential for disease identification, both biomarkers have a number of limitations. Limitations of CA-125 include low specificity, variable sensitivity, and its dependency on the patients lifestyle. Whereas HE4 limitations include reduced sensitivity in early disease, dependency on renal function, and limited endometrial cancer data.

Although these biomarkers have good potential for detecting endometrial cancer, further high-quality studies are needed to accurately determine their diagnostic potential, and to ascertain whether this potential is sufficient to be used in a clinical context.

The emerging technology of omic sciences, which integrates genomics, transcriptomic, proteomics, metabolomics, and more, has been widely used to study complex diseases, due to its broad screening capabilities. DNA-based markers represent the most promising category of biomarkers, with microsatellite instability (MSI) emerging as a critical biomarker for immunotherapy selection. Approximately 25-30% of endometrial cancers show high-MSI, which makes them a good immune checkpoint, which are molecules on our cells that prevent the immune system from attacking it, ensuring an effective response against pathogens and cancer cells. RNA biomarkers (particularly microRNAs) offer additional diagnostic and prognostic information. Despite this, studies in this field are often based on small sample sizes, and hence the validation of these molecular signatures is limited.

Another key category of biomarkers are proteins and metabolic markers. Proteomic approaches have identified numerous candidate biomarkers through analysis of tissue and serum samples. Multi-protein panels combining traditional markers with novel candidates show improved diagnostic performance compared to single biomarkers. Comparatively, metabolomics analysis reveals distinct metabolic signatures associated with endometrial cancer. This includes altered glucose metabolism, lipid synthesis, and amino acid processing pathways that characterise tumour progression to malignancy.

Specifically, the PTEN tumour suppressor pathway, a key pathway in regulating cell growth and division, represents one of the most frequently altered pathway in endometrial cancer, with PTEN loss occurring in 34-55% of cases. PTEN mutations activate the PI3K/AKT/mTOR pathway, making these tumours potentially susceptible to targeted therapies including mTOR and PI3K inhibitors. Hence, PTEN is increasingly used for molecular classification and treatment selection.

Additionally, angiogenesis markers, including various VEGF pathway components, offer insights into tumour vascularity and the potential response of a tumour to anti-angiogenic therapies. Furthermore, novel angiogenic factors beyond VEGF are being investigated as both biomarkers and therapeutic targets, particularly in the case of advanced or recurrent disease. Other emerging biomarkers include hormone receptor variants beyond traditional oestrogen and progesterone receptors, as well as immune-related biomarkers.

Finally, the integration of artificial intelligence and machine learning is revolutionizing biomarker discovery by identifying complex patterns in multi-omics data that may not be apparent through traditional analysis methods. Several studies have focused on the use of machine learning in endometrial cancer, however the results suggest minimal improvement compared with traditional statistics, implying that machine learning may not gain widespread use in endometrial cancer, but further studies are required. It has the potential for early disease diagnosis and personalised therapeutic treatments.

Despite promising research findings, several challenges impede clinical use of these emerging biomarkers. A key issue is the sample size: overall studies in this field were based on small sample sizes, which limits validation of the results, and discrepancies in methodology can strongly influence the result of such small studies. A second challenge is that assays can become complicated for certain biomarkers, raising the cost and resulting in difficulty reproducing of these experiments.

To summarise, the future of endometrial cancer biomarkers lies in integrated, multi-dimensional approaches. Combining different biomarkers will likely provide superior performance compared to single markers. This precision medicine approach represents a paradigm shift from the traditional "one-size-fits-all" treatment model to personalised therapeutic strategies. As biomarker discovery continues to advance, the integration of these molecular insights with clinical parameters will further refine risk stratification and treatment algorithms, which can be used to inform treatment and prognosis. This in turn provides information about an individuals specific disease state and hence treatment plans and drugs can be tailored.

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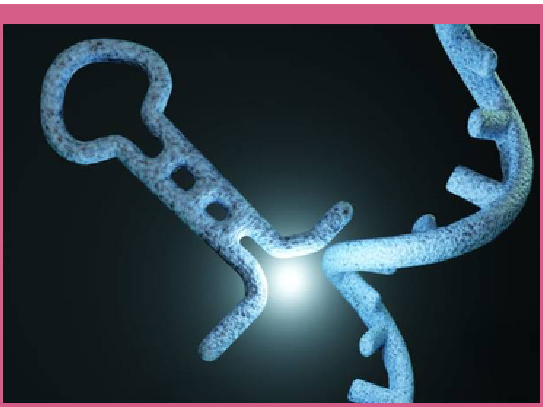
MicroRNA Biomarkers and AI-Enhanced Sequencing in a Two-Stage Model for Cancer Detection

by Hannah Sandhu



Introduction

Cancer remains one of the leading causes of death globally, responsible for nearly one in six deaths1. In 2020 alone, there were an estimated 19.3 million new cancer cases and 10 million cancer-related deaths worldwide2. Despite significant advancements in oncology, the global cancer burden continues to grow, largely due to population aging, environmental factors and lifestyle changes.

Early detection is key to improving long-term prognosis, enabling curative treatment at a stage when tumours are small, localised and more responsive. However, current detection strategies remain suboptimal. These include imaging techniques such as CT, MRI and PET scans, various lab tests including tumour marker analysis and tissue biopsies- often considered the diagnostic gold standard3. While useful, these methods are limited by various factors: imaging lacks molecular resolution, tumour markers are often non-specific or elevated only in late-stage disease, and solid biopsies are invasive, resource-intensive and not always feasible due to tumour location or patient comorbidities.

Therefore, there is an urgent need for new diagnostic approaches that are minimally invasive, highly sensitive and capable of detecting cancer at its earliest stages across a broad range of tumour types. These technologies must also be scalable, cost-effective and suitable for routine use in primary care settings, if they are to meaningfully impact population-level outcomes.
This review explores the shifting paradigm in cancer diagnostics- from invasive tissue biopsies to liquid biopsies, and from DNA fragments to more informative biomarkers like microRNAs. It further examines the convergence of artificial intelligence with molecular diagnostics and proposes an integrated, two-stage diagnostic model that could help transform cancer detection and personalise decision-making in clinical practice.

Limitations of Conventional Tissue Biopsy in Oncology

Tissue biopsies, in which a sample of abnormal tissue is surgically removed for histopathological analysis, remain the diagnostic gold standard in oncology. Depending on the cancer type and tumour location, samples may be obtained through various methods. These include needle biopsies for tissues such as the breast, liver or bone marrow; endoscopic biopsies during procedures such as colonoscopy or bronchoscopy; and surgical biopsies, where either part (incisional) or all (excisional) of the abnormal area is removed. In all cases, a pathologist examines the sample microscopically and may perform additional molecular or immunohistochemical tests to determine diagnosis, prognosis and potential treatment pathways.

Despite their diagnostic utility, tissue biopsies present several limitations. Foremost among these is the invasive nature of the procedure. Biopsies carry inherent risks including bleeding, infection and procedural discomfort. For patients with significant comorbidities or tumours located in anatomically inaccessible regions, such as the brain, lung or pancreas, obtaining a biopsy may not be feasible. For example, in one clinical case, a 72-year old man with severe chronic obstructive pulmonary disease (COPD) and a suspected lung tumour was deemed unfit for surgical biopsy due to the high risk of anesthesia-related respiratory complications. Less invasive attempts using transbronchial needle aspiration yielded insufficient tissue, leaving clinicians unable to confirm the diagnosis or initiate targeted treatment.

Moreover, tissue biopsies are subject to sampling bias. Since cancer is a heterogenous disease, a single tissue sample may not reflect the full molecular or spatial complexity of the tumour, potentially leading to inaccurate diagnosis or staging. Another critical limitation is the static nature of the information provided. Tissue biopsies reflect a single time point in the course of disease and are not suitable for real-time monitoring of tumour progression or treatment response. This is particularly problematic in the context of precision medicine, where ongoing molecular assessment is essential for guiding adaptive therapeutic strategies.

The Emergence of Liquid Biopsies as a Diagnostic Alternative

In response to the limitations of traditional tissue biopsies, liquid biopsies have emerged as a promising alternative for cancer detection and monitoring.

This technique analyses tumour-derived material present in blood, including circulating tumour DNA (ctDNA), which consists of fragmented DNA released by cancer cells; cell-free DNA (cfDNA), a mixture of DNA fragments from both normal and tumour cells; circulating tumour cells (CTCs), intact cancer cells that have shed from the primary tumour into the bloodstream; exosomes, small extracellular vesicles that carry proteins, lipids and nucleic acids; and microRNAs, explored further in this article. By using a minimally invasive standard blood draw, liquid biopsies offer the potential for safer, more accessible testing, that enables repeated sampling over time, facilitating longitudinal monitoring of tumour evolution, treatment response and potential relapse. Furthermore, because circulating biomarkers reflect signals from multiple tumour sites, liquid biopsies may offer a more comprehensive overview of disease heterogeneity than a single-site tissue sample.

Among current applications, the Galleri test, developed by GRAIL, is one of the most advanced multi-cancer early detection (MCED) platforms. It employs machine learning to detect abnormal methylation patterns in cfDNA to identify over 50 cancer types. The test demonstrates very high specificity, approximately 99.5 percent4, and accurately predicts the tissue of origin in over 90 percent of cases5. However, sensitivity for early-stage cancers remains modest, often below 30 percent for stage I and II tumours, and diagnostic performance varies by cancer type6. Large-scale trials, including a 140,000-participant study within the NHS are ongoing to evaluate its impact on reducing late-stage diagnoses, with final results expected in 20267. Yet, these challenges have prompted interest in alternative or complementary biomarkers, including microRNAs, which may offer greater diagnostic precision.

The Diagnostic Potential of MicroRNAs (miRNAs) in Cancer

miRNAs are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level. First discovered in the early 1990s, miRNAs were initially dismissed as ‘evolutionary junk’8. However, they are now recognised as powerful regulators of numerous cellular processes, including apoptosis, proliferation, and differentiation, through their influence on both tumour suppressors and oncogenes.

Mechanistically, they function by incorporating into the RNA-induced silencing complex (RISC) and binding to complementary sequences in the 3’ untranslated region (3’ UTR) of target mRNAs, via a conserved seed sequence. This either promotes mRNA degradation or inhibits translation, thereby modulating protein synthesis9.

Under normal physiological conditions, miRNAs help maintain cellular equilibrium by fine-tuning gene expression. They can be thought of as molecular thermostats, constantly adjusting gene activity to keep cellular systems within optimal ranges. When this regulatory system is disrupted- due to epigenetic modifications, altered transcription factor activity, or defects in miRNA biogenesis- miRNA expression becomes dysregulated. For example, upregulation of miR-21 leads to inhibition of tumour suppressor pathways, since it is an onco-miRNA. This can disturb important signalling pathways, promoting tumour initiation, progression, and metastasis.

Due to their central role in tumour biology, miRNAs have attracted significant interest as potential biomarkers for cancer. Several properties make them particularly well-suited to this role. They are small and highly stable in circulation, often protected within extracellular vesicles or bound to protein complexes. They are also cell- and tissue-specific, meaning that their expression profiles can reflect not only the presence of cancer, but also its anatomical origin and molecular subtype.

Unlike broader analytes such as cfDNA, miRNAs offer insight into the active regulatory networks within tumour cells. This specificity positions them as promising tools for integration into liquid biopsy technologies aimed at earlier and more precise cancer detection.

Combining miRNA Signatures with Ai in the miONCO-Dx Platform

The diagnostic potential of microRNAs has led to the development of advanced platforms that harness their expression profiles for early cancer detection. One such innovation is miONCO-Dx, an artificial intelligence-powered blood test developed by Xgenera in collaboration with NIHR. The test uses 10-15 drops of blood from a standard venous blood draw and integrates machine learning algorithms with large-scale training datasets obtained from over 20,000 patients, to identify complex, disease-specific patterns of microRNA expression with high accuracy10.

miONCO-Dx is designed to identify twelve major cancer types, including bowel, lung, breast, prostate, pancreatic, ovarian, liver, brain, oesophageal, bladder, gastric, and soft tissue sarcomas. In early validation studies, the test demonstrated over 99 percent accuracy in distinguishing cancer from non-cancer samples at all stages (I-IV), with the additional ability to predict the anatomical origin of the malignancy, with an accuracy of 98 percent.

Moreover, identifying cancer earlier will also reduce the cost to healthcare providers, not only because treatment at an earlier stage is cheaper, but because of the cost-effectiveness of miONCO-Dx compared to other MCEDs. As well as being financially accessible, the aim is to make this liquid biopsy available to those in socially-deprived and remote areas too 11.

Currently, a large NHS-funded trial involving 8,000 patients is underway to evaluate real-world performance, cost-effectiveness, and clinical utility in routine practice12. Despite its high potential for use in primary care settings, it does have limitations. Unlike gene sequencing, it does not provide mutational data, which may be necessary to guide targeted therapies. Furthermore, certain microRNAs are involved in multiple physiological and pathological processes, which raises the risk of false positives in non-cancer contexts such as inflammation or cardiovascular disease. For example, elevated levels of miR-21 have been associated with both colorectal cancer13 and inflammatory conditions14, while let-7 miRNAs have been implicated in both lung cancer15 and cardiac fibrosis 16.

This functional overlap highlights the need for careful interpretation of expression signatures, and often requires integration with additional clinical or molecular data to increase diagnostic confidence.

Complementing with AI-enhanced Gene Sequencing

While miRNA-based platforms such as miONCO-Dx offer a powerful tool for early cancer detection, they do not provide information about specific genetic mutations that may underlie tumour development or guide therapeutic decisions. To address this limitation, a second diagnostic stage involving AI-enhanced gene sequencing is proposed. When combined, these tools form a two-stage workflow that balances accessibility, sensitivity and molecular depth.

Platforms such as Oxford Nanopore and IIT Indore's Quantum AI Nanotechnology enable rapid, long-read sequencing of tumour DNA and RNA, offering complementary advantages for confirmatory testing. Oxford Nanopore utilises protein nanopores to analyse single molecules in real time: as DNA or RNA strands pass through a nanopore embedded in a membrane, disruption in ionic current corresponds to specific nucleotide sequences17. This approach facilitates ultra-long reads- sometimes exceeding megabase lengths- which improve detection of structural variants, repetitive regions and methylation patterns 18. Moreover, the portability of Oxford Nanopore's sequencing devices like the MinION enables point-of-care applications, and real-time data streaming allows testing to end once sufficient data is gathered. However, despite improvements, nanopore sequencing still exhibits higher base-calling error rates (approximately 5-10 percent) compared to short-read methods, and its accuracy may be insufficient for single-nucleotide variant detection without additional validation19.

In contrast, IIT Indore's Quantum AI Nanotechnology represents an emerging solid-state nanopore-based system enhanced by quantum transport principles and explainable AI. The device measures transverse tunnelling signals as DNA molecules traverse a nanogap, producing distinct electronic signatures for each nucleotide. AI algorithms decode these signals, enabling high-resolution DNA sequencing that can resolve natural, epigenetic and synthetic genetic changes quickly and cost-effectively, addressing limitations of both traditional next generation sequencing and biological nanopore systems20. This method is reported to offer rapid mutation detection with greater accuracy and lower computational demands. However, as a novel technology, it is still early in its translational pipeline and requires further clinical validation and standardisation. Overall, both platforms can deliver comprehensive molecular profiles that inform prognosis, predict treatment response, and identify potential therapeutic targets.

When used in combination, microRNA profiling and genomic sequencing form a complementary diagnostic strategy. MicroRNA tests such as miONCO-Dx offer rapid, non-invasive triage in primary care settings, detecting a broad range of cancers with high specificity and identifying the likely tissue of origin. For patients with positive or ambiguous results, follow-up sequencing provides mutational resolution, helping confirm the diagnosis and guide clinical management.

This proposed two-stage workflow model has the potential to reshape cancer diagnostics by shifting detection upstream into community settings and enabling more personalised, data-driven care. In Stage 1, a patient presenting with vague or non-specific symptoms could undergo a miONCO-Dx blood test via standard venous draw. In Stage 2, if cancer is suspected, the patient would be referred for confirmatory genomic sequencing and specialist evaluation. This model could accelerate diagnosis, reduce unnecessary invasive testing, and improve outcomes through earlier intervention.

However, practical and ethical considerations must be addressed. These include the cost of implementation, the need for clinician training in interpreting AI-generated results, and issues surrounding data privacy and incidental genomic findings. If successfully integrated, this model could represent a major shift toward more accessible, accurate, and timely cancer diagnostics.

Conclusion

The convergence of liquid biopsy technologies, microRNA biomarkers and artificial intelligence marks a critical shift in the future of cancer diagnostics. As traditional approaches struggle to meet the demands of early, accurate and minimally-invasive detection, microRNA-based assays such as miONCO-Dx demonstrate considerable promise in identifying a broad spectrum of cancers with high specificity from a simple blood sample. Their ability to provide information on both cancer presence and tissue of origin represents a significant step forward in diagnostic precision.

However, the diagnostic value of microRNAs is best realised when coupled with complementary technologies that can resolve the mutational landscape of tumours. AI-enhanced sequencing platforms, such as Oxford Nanopore and IIT Indore's Quantum AI system, offer the depth and resolution required to confirm diagnoses, stratify risk, and inform therapeutic decision-making. Together, these technologies support a two-stage diagnostic model that integrates early triage in primary care with detailed genomic analysis in secondary settings.

Implementing such a workflow will require thoughtful integration into existing healthcare infrastructure, alongside attention to cost, ethical data management, and clinical training. Yet, if effectively deployed, this strategy could not only accelerate diagnosis and reduce reliance on invasive procedures, but also enable truly personalised and equitable cancer care.

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Will we ever find a cure for cancer?

by Lucy Robinson

Cancer refers to a diverse family of pathology with more than 200 subtypes, characterised by the excessive proliferation and spread of a somatic cell. Cancer affects 1 in 2 people born in the UK during their lifetime and, with more than 1,000 people diagnosed with cancer every day in the UK, understanding the causes and mechanisms involved in cancer becomes ever more crucial to improve existing treatments and develop new, more specific, and more effective treatments.

Curative cancer treatments aim to eliminate all cancerous cells and achieve long-term remission, with the goal of a complete recovery and a normal quality and duration of life. Despite enormous efforts from scientists across the globe, there still is no single 'cure' for cancer. Unlike other diseases, particularly those caused by infectious agents, cancer originates from healthy cells. Different modalities of cancer treatment, primarily surgery, radiotherapy, chemotherapy, and immunotherapy, aim to exploit differences between cancer cells and healthy tissues and therefore minimise off-target effects. Instead of a single one-size-fits-all cure, clinical cancer therapy uses a plethora of different approaches. An individualised approach is therefore crucial to effectively treating this highly diverse group of diseases.

I hope to explain some of the reasons why traditional cancer therapies fail and why personalised combination therapies, based on molecular processes, can improve patient outcomes and potentially offer a 'cure'.

Basic arms of cancer therapies

45% of cancers diagnosed in the UK are treated with surgery and surgery with total tumour resection can be curative, particularly if cancer is diagnosed early. However, anatomical location of the tumour can limit the efficacy of surgery, and it is largely ineffective against multiple, metastasised cancer, though may provide some symptomatic relief.

On the other hand, radiotherapy induces DNA damage through a direct pathway (electrons directly cause damage) and an indirect pathway (through free radical production). This technique is used for non-resectable, localised tumours , or in combination with surgery. Radiotherapy affects both cancer cells and the immune response to cancer—offering the possibility of radiotherapy and immunotherapy combination therapy. However, much like surgery, the use of radiotherapy is limited by anatomical tumour location, particularly for tumours of the central nervous system.

While surgery and radiotherapy represent most of the 'curative' treatments, chemotherapy (using drugs to target non-resectable or disseminated disease) and immunotherapy (which helps the immune system become more active and effective at finding and destroying cancer cells) are crucial treatment modalities.

Challenges of cancer therapeutics (and why existing treatments fail)

Due to cancer originating from (and sharing many characteristics with) healthy tissues, it is extremely difficult to selectively target cancer cells. The majority of chemotherapy drugs target cell division and therefore in addition to just cancer cells, these drugs inhibit the growth of rapidly dividing cells. This affects tissues with high growth rates—including hair, skin, gastrointestinal tract and bone marrow. While hair loss and nausea are the stereotypical side effects of chemotherapy, neutropenia (the systemic depletion of white blood cells) can result in increased susceptibility to opportunistic infections and also affects the tumour-suppressive role of the immune system.

The reversible and irreversible toxicities of these drugs determine recovery time between cycles and maximum safe cumulative exposure, respectively.

The diversity of cancer poses an enormous challenge to cancer treatment; not only are no two tumours the same, but there is heterogeneity within any single tumour, meaning that different subpopulations of cells within a single tumour exhibit different characteristics and susceptibilities to treatment. Additional differences in anatomical location and stage mean that tumours of the same type can vary massively in their response to treatment.

Much like many infectious organisms, tumours are rapidly evolving due to characteristic genomic instability and dysregulated cell cycle. This leads to an increased frequency of mutations, meaning, much like antimicrobial resistance, tumours are constantly evolving resistance mechanisms, rendering existing therapeutics useless in the fight against disease.

Cancer Genetics

Understanding the specific mutations and their roles within cellular processes offers the possibility of molecularly targeted, personalised cancer therapies. The mutations associated with the development of cancer may be either inherited or sporadic, and facilitate uncontrolled proliferation either directly (through dysregulation of the cell cycle) or indirectly (through a variety of mechanisms including genetic (or epigenetic) instability increasing the occurrence of other mutations). 'Tumour suppressor' genes, most notably p53, Rb and BRCA1, serve important biological functions but when altered through loss-of-function mutations they can facilitate cellular proliferation. Conversely, proto-oncogenes may be defined as genes in which a gain-of-function mutation can drive a cell toward cancer.

Technological advances in sequencing and data processing and analysis facilitate much larger genome-wide association studies (GWAS, such as the ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium (2020)). This have allowed for the identification of many more cancer-associated genes, and their relative contribution to cancers of different types, based on their prevalence within cancer genomes.

Understanding the molecular changes associated with cancer can directly translate to therapeutic benefits. One of the most notable contributions of genomic studies to understanding cancer was the identification of BReast CAncer genes (BRCA genes). BRCA1 and BRCA2 encode critical proteins involved in DNA damage repair. Both BRCA1 and BRCA2 are crucial for the repair of DNA damage, specifically double-strand DNA breaks via homologous recombination (HR). BRCA mutations are strongly associated with increased risk of breast cancer; inherited BRCA mutations are associated with a 60% risk of breast cancer compared to 13% lifetime risk in the general population. In addition to an increase in overall lifetime risk of breast cancer, BCRA mutations are associated with earlier onset, more aggressive disease and a greater risk of relapse. Inherited BRCA mutations are somatic, meaning they are present in all body cells and therefore can be detected via a blood or saliva sample. Individuals who have inherited a harmful change in either BRCA1 or BRCA2 are recommended to start breast cancer screening at a younger age and participate in an enhanced screening programme, including MRI in addition to mammography, and may be offered prophylactic risk-reducing surgery (e.g. bilateral risk-reducing mastectomy or salpingo-oophorectomy) or chemoprevention. Tamoxifen and raloxifene are FDA approved to reduce breast cancer risk in women who have an elevated risk of breast cancer indicated by their personal and family medical history.

Antibody-drug conjugates

Monoclonal antibody drugs, such as trastuzumab (Herceptin) and imatinib allow specific features of cancerous cells to be targeted, limiting damage to healthy tissues.

The Philadelphia chromosome is a reciprocal translocation between chromosomes 9 and 22 implicated in 90% of chronic myeloid leukaemias resulting in constitutively active tyrosine kinase, which drives myeloid cell proliferation and CTL. The Philadelphia chromosome may be selectively targeted by imatinib, a small molecule inhibitor of BCR-ABL, illustrating how understanding of molecular mechanisms can directly translate to therapeutic benefits.

PARPi (Poly ADP Ribose Polymerase Inhibitors)

Olaparib (Lynparza) is another targeted therapy, meaning it specifically targets cancer cells with certain genetic mutations, particularly BRCA1 or BRCA2 gene mutations. PARP proteins are crucially involved in the repair of DNA damage (specifically the repair of DNA single-strand breaks (SSBs) mediated via the base excision repair (BER) pathway). In healthy cells with an intact HR pathway, DNA damage can be repaired effectively, however in tumours with homologous recombination repair deficiencies (such as those with BRCA mutations) PARP inactivation results in DNA collapse and apoptotic cell death. This enhanced specificity to PARP inhibitors because of mutations is known as synthetic lethality.

Cancer is a microevolutionary process driven by multiple mutations. These mutations may be either inherited and sporadic, and facilitate uncontrolled proliferation either directly (through dysregulation of the cell cycle) or indirectly (through a variety of mechanisms, including genetic (or epigenetic) instability increasing the occurrence of other mutations). While this process depends on the same principles of mutation and natural selection, it operates on a much shorter timescale, meaning that mutations accumulate within the human lifespan. Cancer is, therefore, predominantly a disease of the elderly, with cancer prevalence increasing with age and 36% of new cancer cases (excluding non-melanoma skin cancers) in those aged 75 and over in the UK. Rapidly evolving tumours with multiple mutations can result in treatment resistance and can limit the efficacy of molecularly targeted therapies. Understanding the mechanisms and drivers of this increase in genetic instability (and resulting accumulation of mutations) may help to slow cancer progression and may therefore offer the opportunity for therapeutic intervention.

There is no one-size-fits-all approach to cancer therapeutics: historically cancer treatments cause a great deal of dose-limiting side effects, in addition to the emergence of therapeutic resistance (due to rapidly mutating tumours). Greater understanding of the molecular changes associated with the development of cancer allows for improved specificity and reduced toxicity of cancer therapies. Cancer survival is improving; cancer survival in the UK has doubled since the 1970s. This is in part due to recent developments and improvements in existing therapies (such radiotherapy adjuvants which selectively increase the radiosensitivity of tumours) and increasingly personalised treatment plans: the increasingly widespread use of next-generation sequencing, for example, allows specific mutations to be identified and treatment plans to be adjusted accordingly.

However, there is still a long way to go to completely ‘cure’ cancer. It is important to recognise not only differences between cancer types, but also diversity and heterogeneity within individual tumours. Moreover, personalised treatment comes at a cost, exacerbating inequality in treatment access globally.

While there is unlikely to be a ‘cure’ in the near future, the future of cancer therapeutics is, however, bright.

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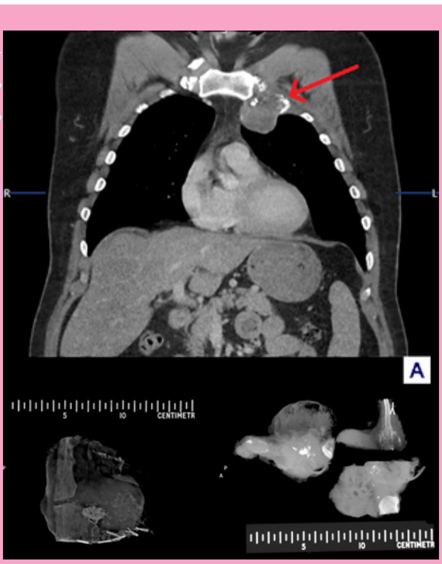
Integrating Precision Pathology and Tailored Surgery for Improved Outcomes in Thoracic Chondrosarcoma

by Julius Bulio

Figure 1: CT scan that the patient had before the surgery and the specimen post-sugery



Introduction

The integration of precision pathology with personalised surgical techniques is fundamentally reshaping thoracic oncology. These innovations have allowed clinicians to move away from a one-size-fits-all approach and towards tailored, evidence-based management plans that account for each tumour's unique biological and anatomical features. This shift was exemplified in a case I observed during my final year of medical school on a cardiothoracic surgery rotation. The patient, a 54-year-old Royal Navy serviceman, was diagnosed with a high-grade chondrosarcoma of the left anterior chest wall. This aggressive cancer, which arises from cartilage-producing cells, extends into the thoracic cavity and presses against vital blood vessels. This proximity to key structures made surgical removal and cancer management exceptionally challenging.

The patient initially presented with a two-month history of progressive discomfort and swelling over the anterior left chest. Examination revealed a palpable, firm, and slightly tender mass. Cross-sectional imaging, including CT and MRI, identified a 59 × 45 × 63 mm (Figure 1) partially calcified lesion arising from the anterior chest wall, with radiological features suggesting invasion of the internal mammary artery. Subtle radiodensities along the biopsy tract suggest tumour seeding, a complication where tumour cells spread during the procedure. Microscopic analysis revealed cellular atypia, meaning the cells appear abnormal in shape and structure, and increased mitotic figures, indicating more frequent cell division than usual; both findings are strong indicators of malignancy. These features suggest a high risk of local recurrence and distant metastasis. Therefore, a personalised medicine approach, tailored to the tumour's specific characteristics, is crucial for optimising treatment outcomes.

Pathology and Molecular Diagnosis

Central to the management strategy was the use of precision pathology, which involves combining detailed tissue analysis with molecular testing to make a more accurate diagnosis. This approach focuses on identifying specific biomarkers (molecules or proteins that indicate the presence or behaviour of a tumour) and guides treatment decisions. Postoperative tests using immunohistochemistry (IHC) of the tumour tissue showed strong S100 protein positivity, which is a typical feature of cartilage-based tumours and an important clue for diagnosis 1. There was also focal expression of ERG (a protein associated with certain bone and vascular tumours), and a Ki-67 index of 12% (a marker showing how many cells in the tumour are actively dividing), indicating moderate levels of cell division and tumour growth. Although periostin, a new biomarker that can help distinguish low-grade chondrosarcoma from a benign tumour called enchondroma, was not used in this case, research shows it could be a useful marker, with a specificity of 87% and sensitivity of 70% 2,4. This highlights the crucial role of precision pathology in understanding the behaviour of tumours and improving diagnostic accuracy.

Precision pathology is not just used to confirm a diagnosis but also provides prognostic information, helping to determine how aggressive surgery should be and how closely patients should be monitored afterwards. This is largely achieved through molecular profiling, which involves analysing the tumour's genetic and molecular features to identify specific mutations or patterns. For example, next-generation sequencing (NGS) panels can detect recurrent mutations in the isocitrate dehydrogenase genes (IDH1 and IDH2), present in about 50–80% of central chondrosarcomas. These mutations cause the build-up of an abnormal molecule, D-2-hydroxyglutarate, which disrupts normal cell development and promotes tumour growth. Identifying IDH mutations not only confirms the diagnosis but also points to possible targeted treatments that are being explored. Molecular profiling may also include detecting changes in DNA methylation patterns and gene fusions, offering deeper insights into the tumour's biology and helping distinguish more aggressive tumours from those that are slow-growing. Such data are increasingly influencing surgical planning and overall patient management.

Surgical Approach

Given the tumour's complexity, a hybrid surgical strategy was employed, combining minimally invasive and open techniques. The goal was an 'en bloc resection', meaning complete removal of the tumour in one piece with clear margins (Figure 2). The procedure began with video-assisted thoracoscopic surgery to assess how far the tumour had extended into the chest (intrathoracic extension) and to evaluate whether it could be safely removed (resectability). Once it was clear that the internal mammary artery was involved and there was pleural infiltration, the operation was converted to an open anterior thoracotomy (open chest surgery) for full tumour excision. Intraoperative findings revealed tumour deposits along the biopsy tract and within surrounding soft tissue, requiring a wider excision. Our cardiac surgeon assisted with vascular dissection, ensuring safe removal and haemodynamic stability. Chest wall reconstruction used Permacol™, a porcine-derived acellular dermal matrix that offers excellent biocompatibility and support, reducing the need for more invasive harvesting of the patient's own tissue, such as latissimus dorsi (a large back muscle) or rectus abdominis (the "six-pack" abdominal muscle) flaps, which would increase donor site morbidity and operative time. This approach maintained chest wall integrity and was in line with Enhanced Recovery After Surgery protocols, which aim to minimise complications and speed up recovery by preserving functional anatomy as much as possible.

Multidisciplinary Collaboration

This case showed how crucial teamwork between different medical specialists is when managing rare and aggressive tumours. Thoracic, cardiac, and plastic surgeons, as well as radiologists, oncologists, and pathologists, worked together to plan and adjust the surgical approach and postoperative care. Regular multidisciplinary sarcoma team meetings were essential for planning the surgery, making decisions during the operation, and managing care after surgery. The patient's recovery followed ERAS guidelines, which focus on reducing complications and speeding up recovery. This included early movement, using different methods to control pain, and removing surgical drains based on a set protocol (protocol-driven approach). This means following a carefully planned set of steps, rather than relying only on clinical judgement, to decide when drains can be safely removed to reduce infection risk and support healing. The patient was discharged on the sixth postoperative day without major complications. Because of the aggressive tumour type and involvement of the biopsy tract, meaning cancer cells had spread along the path made by the needle biopsy, increasing the risk of local recurrence, a strict follow-up plan was created. This included imaging every 3–6 months to check for early signs of recurrence or cancer spread.

Reflection and Conclusion

In the future, using more biomarkers like periostin along with molecular profiling (such as testing for IDH mutations) may improve diagnostic accuracy and help assess a patient's risk. Incorporating artificial intelligence (AI) into imaging could make it easier to map out the tumour before surgery, predict the best surgical margins, and detect micrometastases (tiny groups of cancer cells that have spread from the original tumour and are too small to be seen on scans but can later grow into new tumours). Further studies are needed to assess the long-term performance of Permacol™ reconstruction, particularly its durability and ability to resist infection in oncological resections (surgical removal of cancerous tissue). There is also growing interest in acellular matrices (biological scaffolds made from processed tissue with all cells removed) combined with growth factors or stem cells to help rebuild the chest wall and improve function after surgery.

From my perspective, this case was both formative and inspiring. It demonstrated how surgical innovation, precise pathology, and team-based decision-making can significantly improve outcomes for patients with complex malignancies. High-grade thoracic chondrosarcoma is an aggressive cancer that develops from cartilage-producing cells in the chest wall. It grows quickly, often invades nearby tissues such as blood vessels and the lungs, and carries a high risk of spreading to other parts of the body. This makes it exceptionally challenging to treat. My hands-on exposure during this case reinforced my aspiration to pursue a career in oncology, particularly in translational medicine and surgical oncology. The evolving management of high-grade thoracic chondrosarcoma through precision pathology, molecular diagnostics, innovative reconstruction techniques, and multidisciplinary collaboration showed me how we can now deliver patient-centred and outcome-driven care. As these approaches continue to advance, they offer the promise of not only improving survival rates but also enhancing the long-term quality of life for patients facing these formidable tumours.

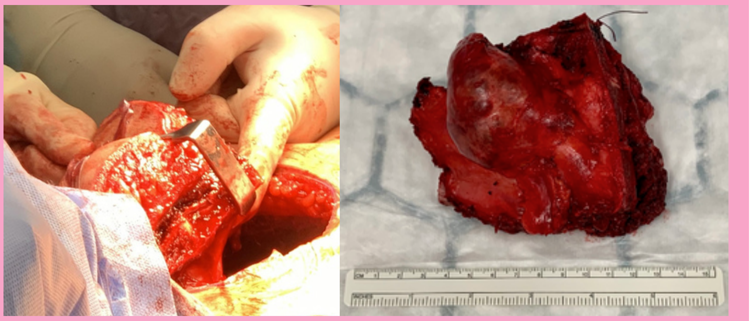
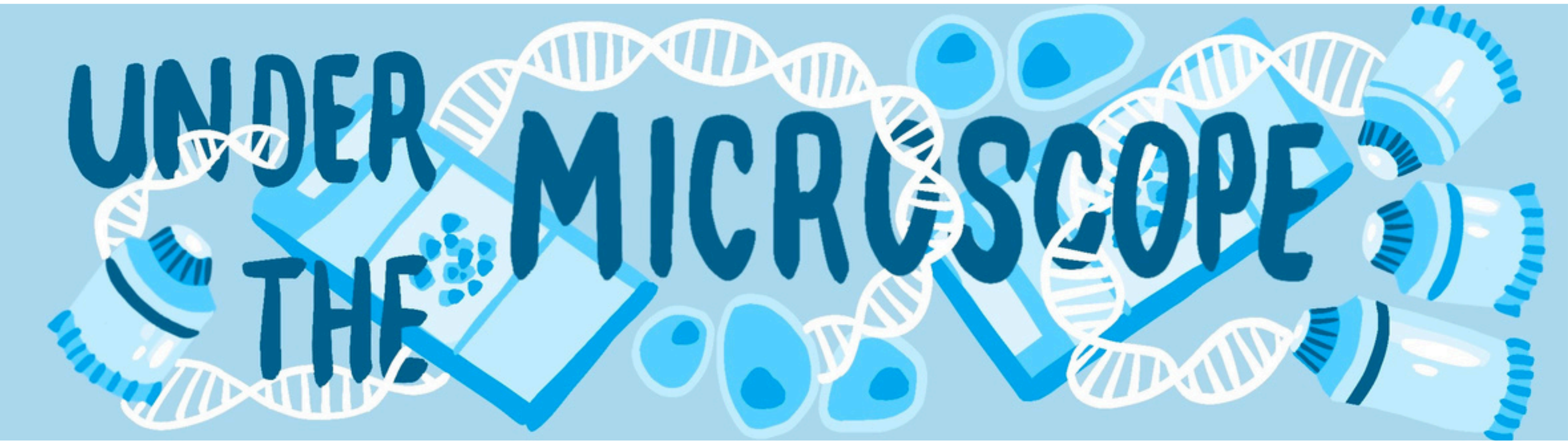


Figure 2: En bloc resection of the tumour



UNDER THE MICROSCOPE

Personalising The Microbiome

by Larissa Chan

Medicine and biology are increasingly adopting an interesting perspective – the ‘holobiont’ - which considers the host and its microbial community (the microbiome) as an emergent whole. In recent years, microbiome-based therapies such as faecal microbiota transplantation (FMT), probiotics, and prebiotics have emerged as promising interventions aimed at restoring or enhancing gut health. FMT, for instance, has proven highly effective in treating recurrent Clostridium difficile infections by re-establishing a healthy microbial balance. However, these approaches often rely on standardised treatments that may not account for the deeply individualised nature of the human microbiome, which leads to a range of nutritional, physiological, and health-related outcomes that extend far beyond genetic differences. By taking personalisation into account, clinicians can tailor behavioural and clinical interventions to individual patients, leading to more precise and effective care.

There is a growing focus on the relationship between the microbiome and treating cancer. For instance, greater gut microbial diversity has been correlated to improved survival rates in patients undergoing bone marrow transplants. More notably, the gut microbiome plays a significant role in shaping responses to cancer immunotherapy, particularly immune checkpoint inhibitors. Immune checkpoint inhibitors are a type of immunotherapy that block checkpoint proteins, which are proteins produced by cancer cells that dampen the immune system’s ability to attack cancerous cells. Companies like Microbiotica are already pioneering microbiome-based co-therapies for cancers such as melanoma, highlighting the growing commercial interest in personalised microbiome-based approaches.

Furthermore, personalised microbiome-based approaches have a lot of potential in advancing cancer diagnostics and prevention. Research led by Dr. Gunjur’s team has identified 22 microbial strains associated with immunotherapy responses across multiple cancer types, pointing to the potential for tumour-agnostic microbiome-based biomarkers. These biomarkers could revolutionize treatment personalization by guiding therapy choices regardless of cancer type. In terms of cancer prevention, ongoing studies are exploring how gut microbial profiles might help predict cancer risk, especially for hard-to-detect cancers like pancreatic cancer. This opens the door to early, microbiome-informed interventions that could significantly improve patient outcomes.

Beyond cancer, personalised microbiome-based approaches could make treatment planning for a whole host of diseases far more effective. Imbalances in the gut microbiome - known as dysbiosis - have been linked to a growing list of health issues, including allergies, autoimmune disorders, metabolic diseases, and even psychiatric illnesses. Addressing dysbiosis through personalised treatments could therefore be pivotal in both treatment and long-term disease prevention. Additionally, incorporating microbiome data into treatment planning can guide drug selection, dosing, and enhance responses to complex treatments like immunotherapy. The gut microbiome plays a crucial role in influencing how individuals metabolise drugs, which affects treatment efficacy and the extent of side effects. Presently, machine learning models using microbiome data have shown high accuracy in predicting individual glycemic responses - changes in blood sugar levels - compared to models built on genetic data alone. In the future, the integration of AI, personalised medicine, and microbiome data could extend to predicting how patients respond to complex interventions like immunotherapy.

However, despite its potential, personalised microbiome treatments still face significant hurdles. One of the major limitations of personalised microbiome treatment is ironically tied to its greatest strength: the individualised nature of the microbiome means that there is no universal ‘healthy’ microbiome signature, which creates a lack of standardisation. Significant inter-individual variation in gut microbiota leads to inconsistent results within studies and poor reproducibility across different research groups, making it difficult for regulatory bodies like the MHRA to assess these highly varied interventions. Moreover, the field is still in its early stages, meaning much of the current research is preliminary and often based on correlation rather than clear cause-and-effect relationships. Further issues include high costs leading to limited accessibility and ethical concerns regarding data protection.

Overall, personalised microbiome-based approaches have the potential to revolutionise healthcare. There are a plethora of applications beyond the approaches covered in this article, including precision therapeutics, which include microbial-based drugs, engineered probiotics, and therapies targeting microbial metabolites; multi-omics integration, where microbiome data is combined with genomics and proteomics to enable more comprehensive health profiling and more accurate diagnoses; and personalised nutrition, which uses individual microbiome profiles to create tailored dietary recommendations, potentially affecting global issues like obesity. Given current evidence, future potential, and the growing public focus on preventive and personalised healthcare, the personalised microbiome is undoubtedly a field to watch.

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Personalized Medicine and Its Impact on COVID-19 Severity

By Dr. Shrikant Verma

When COVID-19 erupted into a global pandemic in early 2020, the world was not only faced with an unprecedented public health crisis but also with an unsettling question: Why did some people suffer devastating complications, while others experienced little more than a cough? The COVID-19 pandemic has shown the importance of personalized medicine in understanding and managing the severity of a disease. Personalized medicine helps us understand why some people are more likely to get infected, how the disease affects different people, and how they respond to treatment. This methodology incorporates a range of factors, including genetic variants, to enhance clinical decision-making and improve patient outcomes. Comprehensive network-based analysis has identified potential determinants of COVID-19 severity at both individual and group levels. Mononuclear phagocytes have been recognized as pivotal coordinators of immune cells, influencing disease severity, as well as specific genes and metabolites, such as monocarboxylate transporter family genes and α-ketoglutarate. The research findings indicate that targeting central metabolic pathways may serve as an alternative treatment strategy for severe cases.

The advancement of digital personalized medicine has expedited the adoption of precision medicine approaches in the management of COVID-19. The integration of wearable smart sensors, wireless connectivity, artificial intelligence, and the Internet of Medical Things has facilitated real-time phenotyping and high-throughput association studies between omics and phenotypic variation. The digital transformation is set to significantly advance personalized medicine research and implementation, potentially resulting in more effective and customized interventions for COVID-19 patients. In summary, the COVID-19 pandemic has highlighted the necessity for personalized medicine approaches to address the variability in disease severity and outcomes. By integrating genetic, metabolic, and digital health data, researchers and clinicians can develop more targeted and effective strategies for the prevention, diagnosis, and treatment of COVID-19, ultimately enhancing patient care and public health outcomes.

Unequal Impact: A Puzzle of Severity

From the earliest stages of the pandemic, doctors and researchers noticed a pattern. COVID-19's clinical presentation varied drastically from asymptomatic cases to acute respiratory distress, multiorgan failure, and death. Age and pre-existing conditions like obesity, diabetes, and hypertension explained some of this variability, but not all. Even young, healthy individuals occasionally succumbed to the virus, while some elderly patients survived with minimal symptoms.

This discrepancy sparked a deeper exploration into the biological and genetic factors behind COVID-19 severity and opened the door to a major shift in modern medicine: the rise of personalized medicine. Research demonstrates that socioeconomic disparities significantly affect health outcomes, environmental exposure, and susceptibility to climate change impacts.

It's interesting to note that research shows industrial pollution sites often end up in poorer areas, which means these communities face higher environmental risks. During the COVID-19 pandemic, we saw a similar pattern, with lower-income districts becoming hotspots for outbreaks. This highlights how economically disadvantaged groups are more vulnerable to infectious diseases. Climate change also plays a role in deepening inequalities, especially in countries like South Africa. When we try to tackle these issues, sometimes we run into unexpected problems. For instance, if we aim for equal vaccine distribution among different groups, it might actually increase disease risk inequalities. This is because high-risk groups might need much higher vaccination rates to balance things out. Similarly, if we're not careful with how we plan urban parks, we could unintentionally make inequality worse. Finally, the complex nature of these unequal impacts is influenced by factors such as income inequality, environmental exposure and resource access. To address these disparities, we need comprehensive strategies that consider the complex interactions between social, economic, and environmental factors, while also being mindful of any unintended consequences of our efforts.

Understanding COVID-19 Through a Personal Lens

Personalized medicine, or precision medicine, is all about tailoring disease prevention and treatment to fit individual differences in genes, environment, and lifestyle. The COVID-19 pandemic really pushed this field forward. Researchers quickly found that genetic differences could help explain why people respond differently to the virus. For example, they identified specific gene variations, like those in TLR7, which are crucial for antiviral immunity, that were linked to severe cases in some young males. Other studies showed that certain HLA genotypes, blood types (especially type A), and even the levels of interferon response genes were associated with different outcomes in COVID-19 patients.

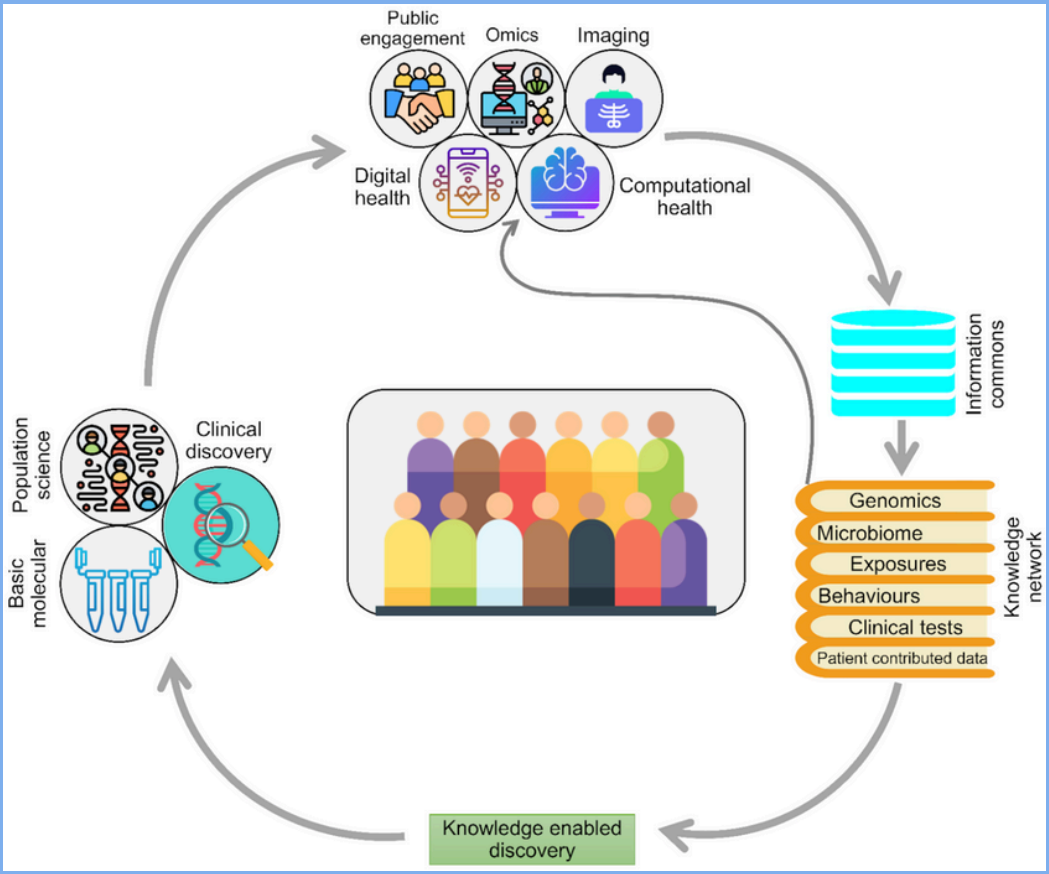
Genetic factors significantly influence an individual's susceptibility to SARS-CoV-2 infection and the severity of COVID-19. This genetic impact on COVID-19 outcomes underscores the potential for personalized approaches to prevention and treatment. Notably, the genetic architecture of COVID-19 susceptibility and severity is complex and not fully understood. Common genetic markers only explain a small part of why some people are more susceptible or have more severe symptoms; rare genetic variants can have a big impact. In young, otherwise healthy individuals who end up with severe cases of COVID-19, about 1-5% have monogenic risk factors affecting interferon signaling pathways. This includes things like X-linked TLR7 deficiency, which are essentially inborn errors of immunity. Discovering these can lead to targeted genetic screening and personalized treatment plans.

In essence, by understanding someone's genetic makeup, we can gain valuable insights into their risk of severe COVID-19 and tailor prevention and treatment strategies just for them. When we combine genetic information with other factors like age, sex, and existing health conditions, we can create more accurate risk prediction models and develop more personalized therapeutic approaches. As we continue to learn more about the genetic underpinnings of COVID-19, it opens up the possibility for more personalized and effective disease management, which could even extend to other infectious diseases in the future.

Biomarkers and Risk Stratification

The pandemic pushed us to develop tools that use biomarkers to assess how severe a COVID-19 case might get. Blood markers like D-dimer, C-reactive protein (CRP), IL-6, and ferritin levels became key players in hospital triage protocols. They helped doctors predict how the disease would progress and allowed them to tailor treatments accordingly.

On top of that, machine learning and artificial intelligence (AI) played a big role in personalizing risk predictions (Khalifa et al., 2024). By training algorithms on patient data sets, which include



everything from medical histories to imaging and genomic,s clinicians could pinpoint high-risk patients, suggest early interventions, and even guide the use of therapies like monoclonal antibodies or corticosteroids.

Tailored Therapies and Trials

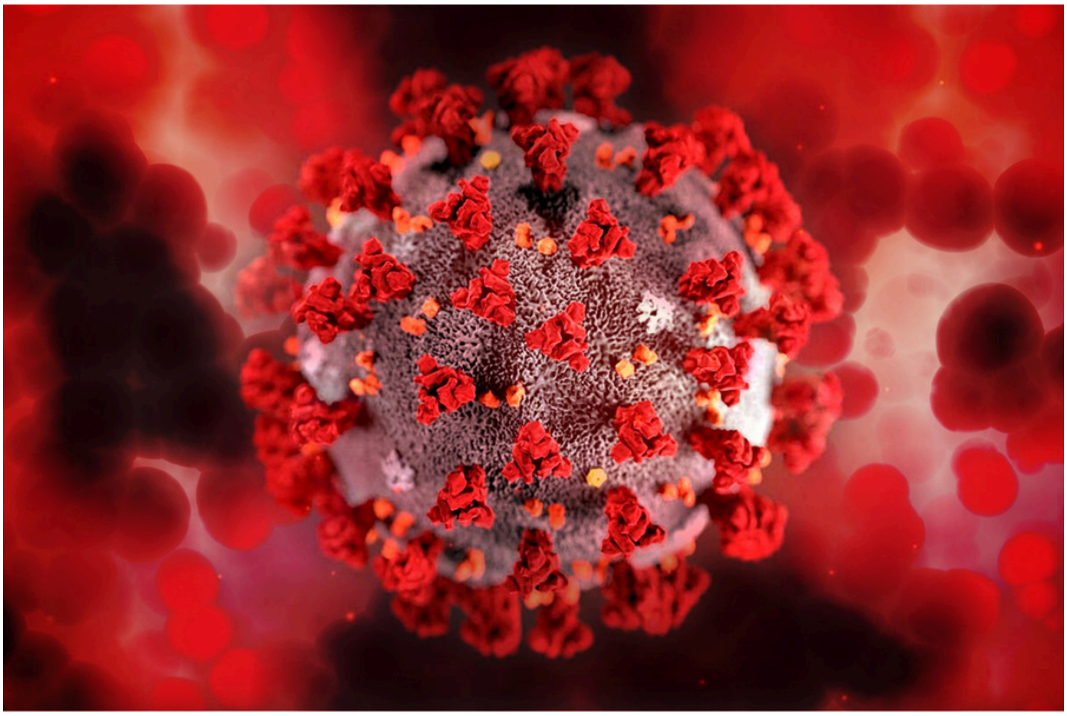
When researchers began using adaptive clinical trials, the approach to COVID-19 treatment became much more personalized. Take the RECOVERY trial in the UK: It cleverly used data-driven subgroups (hospitalized with Covid-19, and randomly assigned patients to receive oral or intravenous dexamethasone). However, it didn't have the same impact on those with milder symptoms (Recovery collaborative group, NEJM, 2021). This really underscores a key principle in personalized medicine: providing the right treatment to the right patient at the right time. Additionally, treatments like convalescent plasma, antiviral therapies, and monoclonal antibodies were tailored based on specific patient factors such as viral load, stage of infection, and immune status. For patients with weakened immune systems, long-acting monoclonal antibody combinations like Evusheld were used as a pre-exposure preventive measure, once again demonstrating a personalized approach based on individual vulnerability.

Long COVID and the Next Frontier

Following the initial infection, it is observed that many individuals continue to experience long COVID, a complex condition characterized by a variety of symptoms such as fatigue, brain fog, and even heart and digestive issues. It appears that a one-size-fits-all approach to treatment may not be entirely effective in this context. This is where personalized medicine becomes particularly valuable. Researchers are diligently engaging in studies that examine immune profiles, the activity of the autonomic nervous system, and the composition of the microbiome to gain a more comprehensive understanding of this syndrome and its treatment. They are thoughtfully exploring customized rehabilitation plans, therapies that modulate the immune system, and interventions for cognitive issues.

Lessons Learned and the Future Ahead

One thing the COVID-19 pandemic really brought to light is that diseases don't affect everyone in the same way, and our treatments shouldn't be one-size-fits-all either. What once seemed like a futuristic concept, personalized medicine has now become a key part of how we handle infectious diseases. The lessons we've learned from COVID-19 are likely to influence how we tackle other complex conditions, like cancer and autoimmune disorders. By combining genomics, data science, and clinical care, we're shifting away from the old trial-and-error methods toward a more precise, individualized approach. In this new era, medicine isn't just about saving lives; it's about tailoring care to match each patient's unique biology.



Not Your Cup of TB? A Personalised Approach to Treating Drug Resistant Tuberculosis Infections

by Lauren Laughlin

Tuberculosis (TB) is a disease that has been afflicting human populations for thousands of years, each exposure beginning with inhalation of droplets from the cough or sneeze of a contagious individual and leading to chronic infection of the lung. In 2023 an estimated quarter of the world's population were infected with Mycobacterium tuberculosis, the bacteria which causes TB. For industrialized countries like the United Kingdom, the Bacille Calmette-Guérin (BCG) vaccine was administered to all school-age children and this has allowed for a substantial decline of TB in the UK, with vaccination now targeted for high-risk individuals. For countries that do not employ this widespread vaccination, TB diagnosis and treatment can be difficult to access which has created an opportunity for the bacteria to grow resistant to the antibiotics established to treat the infection. At an estimated global death toll of around 1.25 million in 2023, tuberculosis regained its title as the world's leading cause of death from a single infectious agent, clearly indicating TB's lethal impact on humans remains and there is substantial work to be done worldwide. We should be looking at what personalised solutions have to offer, and their potential to mitigate the creation of antibiotic resistant strains of TB.

The problem of antibiotic-resistant tuberculosis

Tuberculosis is typically treated by 6 months of a combination of four antibiotics: rifampicin, isoniazid, pyrazinamide, and ethambutol, which target different bacterial processes to kill cells or inhibit their growth. These long treatment plans can be difficult for patients to adhere to and patients may, against doctors' advice, decide to stop taking antibiotics when their symptoms improve and if they start to suffer side effects. Poor quality drugs or incorrect antibiotic prescriptions can also lead to resistance. This is often how antibiotic-resistant strains of bacteria arise – because the drugs will kill susceptible bacteria so there is less competition for space and nutrients for the resistant bacteria, allowing their growth.

Mycobacterium tuberculosis strains can show varying levels of resistance. The high transmissibility of rifampicin-resistant TB (RR-TB) has led to its addition to the critical (highest) group of the WHO priority pathogens list for 2024, identifying this strain as a target for prevention and control of antimicrobial resistant TB. RR-TB strains showing resistance against isoniazid are classified as multi-drug-resistant tuberculosis (MDR-TB). Treatment plans for RR-TB and MDR-TB need to involve antibiotics that the strain is not resistant to – currently WHO recommends the BPaLM (**B**edaquiline, **P**retomanid, **L**inezolid, and **M**oxifloxacin) regimen, lasting only 6 months making adherence to the treatment more likely. However strains showing greater resistance mean antibiotics often need to be taken for upwards of 18 months.

Often bacterial drug resistance is combated by synthesising novel antibiotics. Although, this can take many years and becomes overly expensive - it is not a long-term solution, as bacteria eventually acquire resistance against the new antibiotics. And, making new antibiotics against TB infections is particularly difficult, due to the complex nature of the mycobacteria cell wall which is different from both gram-positive and gram-negative bacterial cells. Therefore, approaches involving personalised medicine to utilise our existing repertoire of antibiotics are vital in preventing the spread of drug-resistant TB.

A personalised approach to drug-resistant treatments

To mitigate the emergence of drug-resistant TB strains, the use of drug susceptibility testing (DST) provides tailored medical regimens for individual patients based on the strain of their specific infection.

Previously, DST was only available through a lab and as mycobacteria are slow-growing so culture results can take upwards of 4 weeks – therefore an initial course of broad-spectrum antibiotics may be prescribed whilst waiting. This is known as empirical therapy, and can be problematic as antibiotics that the bacterial strain is resistant to may be given unknowingly, increasing the resistance of that strain and failing to treat the patient.

Culture Drug Susceptibility Testing

- Sample of mucus containing TB taken from patient
- Bacteria are isolated and grown in the lab
- Different antibiotics are tested on the lab-cultured bacteria
- The ability of each antibiotic to kill the bacteria is summarised in an antibiogram
- Those that worked against the strain are used in a treatment plan personalised to the patient

A faster technique of drug susceptibility testing is the use of rapid point-of-care testing kits, such as Truenat and GeneXpert, which identify sequences of the bacterial genetic code that are unique to resistance genes. For example, the gene rpoB is carried by RR-TB. The antibiotic rifampicin kills bacteria by targeting an essential enzyme. So, the resistance gene rpoB encodes an alternate version of this enzyme, so rifampicin cannot recognise or inhibit it. These test kits provide drug susceptibility results in less than 24 hours, meaning treatment regimens can be put into place almost immediately, whilst waiting for the results from the more reliable culture method.

Personal information can also inform the ideal regimen for a patient's most effective treatment. Their past infection history gives information on previous bacterial infections and may indicate if a latent infection has reactivated and will have pre-existing resistance to certain antibiotics. Evaluating how likely an individual is to adhere to long duration antibiotic regimens can also be a factor of consideration. Weighing the ability to complete consistent monitoring and shorter treatment plans should be considered for the highest likelihood of the patient completing treatment. This information can also be useful in predicting possible adverse effects different treatments may incur; side effects are more frequent in treatment for tuberculosis as antibiotic courses are long-lasting, such as long-term isoniazid causing liver toxicity. Clinical history may also inform healthcare teams about pre-existing immunocompromising diseases that could complicate treatment regimens and lead to a higher likelihood of developing TB primary disease;; particularly for those who have HIV/AIDS or who are malnourished.

Global Personalisation

Whilst personalised medicine is typically used in the context of treating individual patients uniquely, it can also be applied to the needs of individual countries. TB is a disease that can infect anyone, yet 56% of the worldwide total of those suffering from the TB primary disease are located in only five countries: India, Indonesia, China, the Philippines and Pakistan. Examining trends on how the bacteria is spreading in these countries and preventing further transmission through national BCG vaccine administration or frequent diagnostic testing, is important in protecting susceptible individuals. And preventing incidence of all tuberculosis infections therefore prevents the spread of drug-resistant TB.

It is also crucial to consider the economic burden that drug resistant tuberculosis is having. It was estimated by WHO in 2024 that 49% of TB-affected households were facing catastrophic costs for treatments – and this cost rises exponentially for those with RR- or MDR-TB as more complex antibiotic courses are required. The ‘WHO End TB Strategy’ formulated in 2014 set goals for reducing TB incidence and deaths and eliminating the economic burden on TB-affected households by 2030. Whilst the 2025 milestones for these were not reached, partly due to the COVID-19 pandemic, these figures are steadily decreasing and there is progress being made toward a TB-free world. It is evident that we have the means to treat this disease, only that we need to defend treatments from antibiotic resistance. Personalised solutions used to treat patients and prevent further rises in antibiotic resistance offer an alternative outcome, one in which we overcomeTB once and for all.

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