IHRF Discussion Document

Advancing genomics research in Ireland

November 2020

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About the Irish Health Research Forum (IHRF)

The IHRF is managed and funded by Health Research Charities Ireland (HRCI). It is a partnership of organisations and stakeholders, guided by a high-level Steering Group, that aims to positively influence health research in Ireland. The Forum considers key health research issues and identifies constructive solutions at two events every year.

This latest event is on the topic of genomics research, which has the power to unlock better and more personal healthcare for millions of Irish people. It will focus on what Ireland needs to do to harness that potential and we hope for it to be the first of two IHRF events on this important topic.

About Health Research Charities Ireland (HRCI)

HRCI is the national umbrella organisation of charities active in medical and health research, together representing over 1 million Irish patients. Its 40 members span many areas of health, including rare diseases, cancer, childhood illnesses, dementia and many forms of chronic illness and disability. Through support and advocacy, HRCI represents their joint interests, working with them and the wider health research community to improve health and prevent illness through research.

HRCI runs the Joint Funding Scheme in partnership with the Health Research Board (HRB) which offers the opportunity for charities to obtain matched funding in order to support health research of relevance to their communities. HRCI has a strong focus on encouraging and supporting patient and public involvement (PPI) in all aspects of health research.

***Image**: a word cloud of the most commonly used words throughout the submissions below. The largest word was used 186 times and the smallest words were used 9 times.*

Introduction

As the acting Chair for this IHRF event and the CEO of Health Research Charities Ireland which manages the IHRF, we are delighted to run an event on November 12th, 2020 focused on genomics. Given the necessity for this to be an online, shorter than normal meeting, the IHRF Steering Group took the decision to supplement the event with a discussion paper, capturing the views of people with a strong and informed interest in genomics, from across Irish society.

Run by an independent organisation (HRCI), with no agenda beyond putting patients at the centre of health research and overseen by a Steering Group of diverse and strong leaders, the IHRF is ideally placed to facilitate discussions on the big and sometimes challenging issues in Irish health research. This event is no exception. Genomics has become an emotive topic in Ireland in recent times and it is our hope that this discussion paper and the event itself will help to encourage an inclusive, frank and respectful conversation about how Ireland can improve genomics research for the ultimate benefit of the Irish public and patients.

Below are 21 invited submissions from patients and patient representatives, clinicians, researchers, industry representatives and others. We thank them for the thought and time they put into their pieces. Despite views that are strongly held, we see a coherence in the thoughts that have been expressed in them. Together, these pieces offer us a foundation of wisdom on which to build a better future for genomics research in Ireland.

Eibhlin Mulroe
Acting IHRF Chair and CEO Cancer Trials Ireland

Dr Avril Kennan
CEO Health Research Charities Ireland

'The demographic history of the population has resulted in the Irish genome being particularly well suited for studies seeking to identify genetic predictors of disease risk and treatment' *– Gianpiero Cavalleri*

> **'Genomic sequencing needs to be widely available to avoid the anguish of the absence of a diagnosis'** *– Colette Daly*

'Over the next decade, genomic data from many millions of patients will be generated within healthcare globally' *– Mark Lawlor*

> **'Genomics has unleashed a remarkable wealth of information for patients and importantly, the technology is available to translate this information into actionable insights for patients, personalising their care'** *– Mary McGuire*

'For some patients, the information gained from whole genome analysis can save their life; in other cases, it adds new data for potential discoveries to help future patients'
– Verena Murphy and Eibhlin Mulroe

> **'Not participating in this revolution is like throwing our Smartphones/iPhones away'** *– Walter Kolch*

'Whilst the technology increased the sensitivity in analysing DNA and improved the diagnostic yield, it also revealed the extent of human normal variation which took us by surprise' *– Sally Ann Lynch*

> **'Genomic information is a modern Pandora's box, holding a promise of contributing to better understanding and treatment of disease but, in the wrong hands, potentially impacting not just our own lives but those of our descendants'** *– Robert O'Connor*

'Sharing of genomic data needs a balance between the benefit of sharing information in the research community, and the need to respect a research participant's privacy'
– Andrew Green

> **'A partnership of public institutions and commercial collaborators can, with safeguards, ensure that there is appropriate return to each, and to the primary investor – the patient/volunteer and their families'** *– Paul Harkin*

'In return for allowing access to their data a patient could receive shares which they could use as payment for future healthcare services…' *– Oran Rigby*

> **'We must continue to nurture the goodwill of the public and impart confidence by ensuring clear and full consent'** *– Laura Brady*

Submissions on the topic of advancing genomics research

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Dr Laura Brady

Head of Research at Fighting Blindness

Patients are at the centre of retinal genomics research in Ireland

Fighting Blindness and the Irish community has played an essential and expansive role in driving research into inherited retinal diseases (IRDs). Highly heterogenous, these are amongst the most genetically complex of all rare conditions and impose a significant socio-economic burden in Ireland. People with an IRD experience progressive vision loss that can impact on every aspect of life; both on a day-to-day basis but also across one's lifespan.

Ireland's journey started almost 40 years ago when a group of families affected by IRDs took it upon themselves to get the necessary research off the ground. Driven by passion and a quest for knowledge, their goal was clear: to find treatments and cures. Today, Fighting Blindness is the largest charity funding retinal research in Ireland. Largely supported through grassroots donors and those with the greatest stake in its success, the organisation has invested €20 million towards this mission.

Irish researchers have emerged as pioneers and global leaders in the field. In the late 1980's, scientists at Trinity College Dublin studied a large Irish family and described one of the first genes to be linked to an IRD. This landmark genetic breakthrough, not possible without patient participation, brought momentum to the international search for more genes. Today, over 300 IRD genes have been identified which has transformed our understanding of vision loss and led to the development of therapeutic interventions. Despite this, the genetic causality remains unknown for one third of patients. Research is essential to solving these missing variations and understanding how and why disease presents.

Addressing patient needs, our work has evolved into a multidisciplinary programme called Target 5000 combining scientific discovery and healthcare. Through a national registry, it aims to provide a true diagnosis and genetic counselling to everyone impacted by an IRD. This is even more pertinent as we enter an era of gene-based medicine whereby a molecular diagnosis is required to participate in clinical trials or avail of approved treatments.

However, excellent research can only be achieved so long as the patient whose genomic data is being investigated is protected and at the forefront of benefit. Genotypic data for IRDs is rare, yet more than 2,500 affected individuals and their families in Ireland have shared biological samples to help advance research. Our population genetics is of huge interest to the international retinal community. Not only do we appear to be the source of many founder effects, there are likely to be specific Irish variants.

As such, we must continue to nurture the goodwill of the public and impart confidence by ensuring clear and full consent. The balance between public good and corporate profit needs to be transparent and patient advocacy organisations have an important part to play here. In addition, sharing of research through open and accessible databases will lead to important genetic diagnoses for many more individuals and their families. Genomic findings

can extend beyond any index case, so genetic counselling must also be put in place. Recognising this, Fighting Blindness has supported Ireland's first ophthalmology-specific clinical genetics service.

Retinal genomics research is a true example of fundamental biology enabling innovative technology. However, there is a need for significant investment into capacity building in terms of research and clinical expertise, a review of assessment models for gene therapies and the embedding of a strong genomics infrastructure that will attract clinical trials. A national genomics strategy that is incorporated into Sláintecare and where the programme for government with respect to rare disease is honoured, will undoubtedly lead to more effective research, enhanced clinical care and provide a window of hope and opportunity for those living with genetic disease in Ireland.

Prof Gianpiero Cavalleri

Professor of Human Genetics. 1) RCSI School of Pharmacy and Biomolecular Science 2) the SFI FutureNeuro Research Centre

As Irish clinical genetics goes genomic, let's shape it with and around the citizen

The commitment in the Irish Programme for Government ("Our Shared Future - 2020") to a National Genomics Medical Network signifies a rare opportunity. This is the chance to shape the national genomics landscape in a manner that delivers for Ireland in the decades ahead. Realising that shared future will require careful design, informed by dialogue with, and input from diverse stakeholders, first and foremost, the citizen.

The demographic history of the population has resulted in the Irish genome being particularly well suited for studies seeking to identify genetic predictors of disease risk and treatment. Such discoveries hold great promise, as they aid in more personalised and effective treatments for our loved ones. In this context, the collective Irish genome can be viewed through the prism of a natural resource, but it will take careful planning, investment and a lot of effort to realise an equitable benefit to society.

The National Network commitment presents an opportunity to connect the public healthcare system with our universities and research centres, in a manner that leverages the state investment in genomic diagnostics. Today an individual's genome can be sequenced for a price comparable to a MRI scan, and this cost will continue to drop. As genomics is integrated into our healthcare system, an increasing amount of data will be generated. Clinical datasets, including genomic data, carry value far beyond the initial clinical diagnosis, and via programmes of research, learning can feed back and improve the healthcare system and ultimately, our health and quality of life as citizens. As a state-controlled entity, the National Genomics Medical Network should be provided with governance and clear policy to facilitate transparent and responsible partnership with industry, to the benefit of to the citizen and with equitable return. Such partnerships are critical for the ongoing development and delivery of more precise, safe and effective medicines, and indeed well-structured partnerships could speed access to new medications in the Irish system.

The National Network can also facilitate training of analysts, who will help us extract meaning from these data in the years ahead. Partnered with our medical schools, the network can provide the environment to train the next generation of healthcare professionals, equipping them with a framework to interpret genomic data, in a similar manner to how a knowledge of anatomy facilitates the interpretation of a CT, MRI or x-ray. The current opportunity is further enhanced by the HSE's plans to embrace electronic health records. Patterns in these data can help identify novel and more effective approaches to care. Indeed, discovery in genomics is heavily dependent on the clinical information shared by the citizen and often contained within medical records. Such clinical information is expensive

and in the public system, is paid for by the Irish taxpayer. Value derived from the partnership must be equitable and fed back to the public health system.

But at its core, genomics is about the individual and how their data are used. Realising the potential of the proposed Network requires not only the consent of, but partnership with us as citizens. We need dialogue between all the stakeholders, with the citizen at the heart. In this manner we can develop a sustainable and equitable partnership that will deliver a shared future.

Dr Rachel Crowley

St. Vincent's University Hospital / University College Dublin

Irish Genomics Research - clinical need, consent, use/access

It is estimated that 300,000 people in Ireland have a rare disease, the majority of which are genetic and some of these remain undiagnosed. Thus, there is a clear need for both a clinical genetics/genomics programme and a research programme to identify undiagnosed disease and to deliver personalised medicine for this patient group. The challenges are: the funding model for such a programme; the consent of the patients and controls for genomics databases; the protections already in place for such participants and those that may be required; the access arrangements for research use or clinical service design. Clinicians express frustration at the lack of clinical genetics services, or the ability to perform genomics analysis on a well-phenotyped clinical or research cohort. Patients express frustration at a lack of diagnosis but also concerns regarding the implications of testing for family members. Patients also draw a distinction between academic researchers and industry access to their genomic data when discussing how their data is used. Research governance bodies note sample overlap between studies, for example most trials now have a sub-study looking at genomics or personalised medicine but this should be a centralised database.

The strengths Ireland has for such a programme are its small population with a high prevalence of rare disease with an increased likelihood of identifying clinically-significant variants; Ireland's existing contribution to international research; how well-connected Irish researchers are internationally; and how many representatives of the patient voice there are. The Irish public is very interested in medical research.

I would suggest that Ireland needs to develop a set of standards for genomics research to include a policy on how to manage incidental findings of potential clinical significance, clear guidance on whether data can be traced to an individual/family for future clinical/research contact, a public engagement piece that reassures research participants that their rights and well-being are safe-guarded and a parallel clinical genetics programme to support any research outcomes or incidental findings. Such a policy needs to be as future-proofed as possible. For example there is a discussion around the ability of genomic data to reconstruct a recognisable face, or to make other predictions that could identify the donor; or how should genomic information be re-visited if in later years more disease-associated mutations are known than were recognised at the time of initial testing. These are all topics that have arisen in our Research Ethics Committee discussions regarding genomics. Any group contributing to such a national policy would need to have wide representation including but not limited to: patients, members of the public, industry, academia, geneticists, clinical ethicists, legal, insurance, actuarial, artificial intelligence / machine learning expertise.

Should one of the new national research ethics committees be a single committee for review of genomics studies?

Making such data freely available, in keeping with FAIR data usage, has implications in the genomics field. If a state funds a genomics programme that releases data openly, should industry have access to this without investment? If industry funds it can they limit access? What is the potential for such data to be abused?

All of these points are moot if the Irish public does not accept or engage with genomics research because of a failure of communication or an actual system failure that leads them to believe their data is not secure or could be abused, or that their participation is exposing them or their families to risk of any kind.

Colette Daly

Parent

Sean's story - A family's perspective

When you have the great privilege of becoming a parent, your innate instinct is to protect, guide and cherish this beautiful creation, your child. Your hopes, dreams and expectations flourish with every passing day and your love cushions all the little ups and downs of early childhood. But when our beautiful child Sean was 4 years old, nothing could have prepared us for the devastation that uncontrolled seizures would inflict on our lives. Seizures arrived unannounced, uninvited and unexplained. Our healthy little boy descended into a cycle of seizures, hospitalisations and investigations. Myself and my husband Liam were powerless as we witnessed the horror of uncontrolled seizures increasing from 1 to approximately 40 per day within months. Sean was very unwell, his childhood had been suspended, he was frightened and confused. We searched desperately for an explanation, a diagnosis and most importantly a treatment.

In Our Lady's Hospital Sean was rigorously tested, re-tested, scanned, assessed and monitored. All avenues of diagnosis were explored but nothing revealed the origins of Sean's deterioration. The best we had was ‘intractable epilepsy’, unexplained, drug-resistant epilepsy and this remained his diagnosis for 14 years. As Sean's seizures and medications increased his cognitive function and overall development decreased. He started to lose his skills rapidly, he was assessed as having a global developmental delay and was started in a special education school. This was one of the darkest times for us as parents, we felt an overwhelming grief as we had to let go of our expectations and dreams for Sean. Seizure control was sought with countless combinations of medications, right frontal lobe surgery, VNS implant, ketogenic diet and multiple supplementary treatments and therapies all with minimal effectiveness.

We had so many questions, very few answers and always felt we were missing a piece of the puzzle, we became eager students of a subject we greatly resented. One of the most distressing consequences of having no definitive diagnosis for Sean's condition was that we started to blame ourselves, we analysed and agonised over the first 4 healthy years of his life desperately trying to find a cause, we couldn’t reconcile how seizures had been so particularly catastrophic for Sean, we knew there had to be something else in the equation.

As our search continued our consultant told us about the Lighthouse Project, a strand of the FutureNeuro Centre (SFI Research Centre), who were carrying out a genetic clinical research study into severe epilepsies with accompanying intellectual disability. Sean’s genetic analysis was carried out in conjunction with RSCI and in 2017 some truly remarkable news was delivered to us. Sean did indeed have an underlying genetic basis to his condition. Sean has a rare, non-inherited mutation of the CHD2 gene. I can never fully express the profound effect this information had on our family. We finally had a diagnosis after 14 years of waiting, worrying and agonising. It fills us with tremendous hope, research delivered us a diagnosis and research will be the key to discovering ways to deal with and treat Sean’s condition in the future. Ongoing genomic research in Ireland and beyond is absolutely vital in finding

precision medication, optimum therapies, diets and treatments. Genomic sequencing needs to be widely available to avoid the anguish of the absence of a diagnosis. I hope our story will inspire researchers to embark on this essential journey of discovery. Thankfully Sean is doing a little better in the last few years, but we hold out so much hope that research will enable Sean to reach his full potential, that's all a parent can wish for.

Prof Andrew Green

Consultant Geneticist, Children's Health Ireland and UCD

Human genomics - hope and reality

Human genomics, since the publication of the human genome sequence 20 years ago, has had a major impact on healthcare. There has been a major benefit in a many clinical areas, including diagnosing rare diseases, inherited cancer, inherited heart disease and predicting both responses to, and side effects from, many medicines.

Irish patients have already been part of international genomics collaborations. For example, 500 Irish families have been part of the successful UK and Ireland Wellcome-funded Deciphering Developmental Disorders programme. The DDD project has identified the genetic cause in 4,500 families with children with previously undiagnosed developmental disorders, described a large series of newly discovered genetic disorders, and published over 180 papers, including papers in Nature and Nature Genetics.

It is clear that large scale genomics with international collaboration is by far the most effective way to carry out genomics research. The implementation of human genomics worldwide has been uneven, and in many situations depends on the economic ability of a health service to fund the delivery of genomics, rather than on clinical need.

At least 15 countries, including Estonia, the UK, Canada and China, have set up national genomic initiatives, involving disease registries and large-scale genome analysis, although mostly these initiatives are not yet embedded in healthcare.

Rare diseases are not a niche area. The paradox of rare disease is that each one of the 8,000 rare diseases may be rare, but collectively 8% of the population is affected by a rare disease. In the diagnosis of rare disease, there is a clear economic benefit in early genome sequencing, compared to the economic and emotional cost and duration of a long diagnostic odyssey involving hospital admissions, biopsies, imaging, and multiple genetic/biochemical tests.

The implementation of genomics in diagnosis has brought up a number of contentious issues. When analysing a person's genome for an explanation of their neurologic disease, is there a duty specifically to seek out alterations in other genes that may predispose to heart disease or cancer? The American College of Medical Genetics has recommended such a deliberate search as part of the responsibility of a diagnostic lab. In contrast, the European Society for Human Genetics has recommended that genetic testing should be focussed on investigating the specific clinical question to be answered. The situation for seeking targeted secondary findings in research genomic testing, as opposed to diagnostic genomic testing, is even less clear. Any research genomic findings should be verified in a diagnostic lab before being used to make clinical decisions. The clinical interpretation of genomic findings is also difficult with many variants of uncertain significance likely to be found in every person tested.

If genomic testing finds a gene alteration that may predispose to heart disease or cancer, in a healthy person with no family history of the condition, what is the risk to that person of developing disease? We don't know that answer, and only long term follow up over years of large numbers of people will answer the question.

Sharing of genomic data needs a balance between the benefit of sharing information in the research community, and the need to respect a research participant's privacy. Participants and researchers should be aware that public genomic data, even with no personal identifiers, can be tracked back to an individual, if a small amount of genetic information is already known about that individual.

In Ireland, the current genomics research infrastructure is piecemeal, without national coordination. A national genomics policy is needed urgently, both in the area of clinical and laboratory service provision, and in the area of coordinated genomic research structures and policies.

Dr Finnian Hanrahan

Science Foundation Ireland

Genomics research - a strategic opportunity for Ireland

Advancing genomics research is essential for us to realise the true potential of precision medicine. This cutting-edge area of health research enables understanding of disease and response to treatment in a unique, personalised way. With this knowledge doctors can prescribe the right treatment, at the right time, in the right patient. Precision medicine is already starting to revolutionise medicine, but it cannot be truly realised without significant support for genomics research.

The importance of genomics for Ireland is signalled by a number of key investments by Science Foundation Ireland in this area. For instance, the SFI Centre for Research Training in Genomics Data Science, as part of the €100 million SFI Centres for Research Training programme, was launched on the 5th March, 2019. This investment will produce a cohort of highly trained scientists capable of engaging effectively with the data science challenges involved in realising the transformative potential of genomics across the broad range of its applications.

As well as training up the future talent pipeline in genomics research, SFI believes in bringing together different key players in genomics in order to create the critical mass required to effect real change in this field of research in Ireland and to directly impact patients. An important example of this kind of investment is FutureNeuro, the SFI Research Centre for Chronic and Rare Neurological Diseases. Funded by an award of €8m from SFI, FutureNeuro combines the work of academic researchers and industry to drive proactive, precision and personalised medicine, translating genetic diagnostics to the Irish health system. FutureNeuro researchers are sequencing patients' genomes to identify precise genetic causes and working with industry partners to improve the diagnostic yield of genetic testing. The Centre also employs innovative genetic approaches to work towards transforming the lives of the approximately 800,000 people affected by neurological disorders in Ireland.

In SFI we firmly believe that our investments in genomics research are leading to remarkable advances in this field in Ireland. However, we also recognise that national policies must advance in line with technological advances and the country's strategic needs. SFI believes that there is a significant need for a national genomics strategy, and strongly supports the introduction of a national strategy in this area. SFI would welcome any opportunity to contribute to and assist with the development of a national genomics strategy.

Finally, as part of a national strategy, SFI views engagement with the people of Ireland to communicate the potential health benefits that genomics research can deliver to be crucial. To that end, as part of Science Week 2020 SFI will

dedicate a specific strand of dialogue with young people to have an informed conversation about genomics, and the potential of personalised medicine to healthcare in the future.

Paul Harkin

Member of the general public

Getting beyond bad genes

This contribution is given in a personal capacity as a courtesy to the Irish Health Research Forum. It should be seen as the observations of a single individual who has no expertise in the field. I have observed the benefit that genomic insights can make to provide more targeted and more effective therapies. I am thankful for the public research and commercial enterprise that led to these improvements.

Research – biomedical, clinical or health services – has the potential to improve patient care by ensuring that medical interventions are appropriate and evidence-based. Research participation drives a culture of inquiry and discovery leading to better patient outcomes. Genomic research is likely to bring similar benefit to Irish patients. It comes at a very high price however as it requires patient to make an incalculable in-kind contribution much more than that made by a conventional study participant. It has implications for the individual and for their descendants.

Public and Private Partnership in Genomics

Public bodies are unlikely to ever have the necessary resources to support genomic research and exploit it for the benefit of patients. Private enterprises can mobilise the capital required to conduct genomic research at a scale but require a return on this investment. Neither public research institutions nor private investment enterprises can be expected to work selflessly in the interests of patients. However, a partnership of public institutions and commercial collaborators can, with safeguards, ensure that there is appropriate return to each and to the primary investor – the patient/volunteer and their families.

Preferred Model

It is wrong to criticise private enterprises for having a commercial perspective. Also, it is important that public institutions recognise that they have a duty to the country's citizens to protect their investment. Hence, I favour a two-key model.

Ownership of clinical information and experimental data should be retained exclusively by the public enterprise (effectively in trust for the public). Data analysis, genomic database and model expertise can be retained exclusively by the commercial collaborator. Both keys are required to release the genomic value. Either party is free to withhold their key or to use their asset in any another collaboration but to capture a return on this investment, they are incentivised to collaborate.

All other costs of genomic research can be shared by agreement between both parties. They may choose to adjust the relative share of any financial return in proportion to their relative risk burden. However, it is the patient/volunteer whose genetic material is being collected who makes the greatest contribution. Hence the value of the public investment should never fall below a certain specified minimum.

Private enterprises assemble capital with a view to generating a return through licensing their know-how or access to patient data. They will either sell equity stakes to other investors or license their technology to, for example,

pharmaceutical research companies to support the development of targeted therapies or simply to segment the market for existing medicines.

Public research investigators must conduct themselves to the highest ethical standards and not allow themselves to become unwittingly involved in a conflict of interest by enabling the commercial collaborator at the expense of the public. It would be preferable if individuals involved in genomic research are not involved in the contract management on behalf of their institutions or participate in research advisory committees.

Governments should in the first instance protect the public and in the second ensure the public's investment brings benefit to the public. It must not place short term foreign direct investment opportunities or employment benefits over these public protection and beneficence responsibilities.

Dr Anne Jones

COO, Genuity Science

Genomics in Ireland: an industry perspective

Public-Private partnership models are vital to the creation of vibrant and sustainable genomics ecosystems. The need for trust, transparency and equity between public and private organisations who collaborate on genomic programmes cannot be overstated. To engender the trust and confidence of patients and participants who volunteer to take part in genomics research it is important that policy formation in this arena is balanced, transparent and patient centric in its approach. New treatments for disease arise not through the singular efforts of public or private organisations working in isolation, but rather, through strong partnerships that strive to balance carefully the interests of patients and the optimal way to progress science at speed in a way that is beneficial to all participants.

At Genuity Science, we are responsive to this delicate balance and have learned by working closely with patients, our healthcare and university partners, in Ireland and internationally, privacy regulators and our pharmaceutical and biotechnology clients. These constructive dialogues enable us to evolve carefully our policies on important topics such as data ownership, data sharing, responsible management of secondary findings arising in genomics research, intellectual property management and protection of the privacy and transparency rights of individual genomics research participants.

Irish people are already benefiting from Public-Private collaboration in genomics an example of which is Genuity Science's pro bono collaboration with CHI at Temple Street which has seen enrolment of over 200 families and over 20% of cases receiving genetic findings of clinical significance.

Reflecting on five years of operation in Ireland there are several areas where we believe development and investment would enhance Ireland as a location to undertake world leading genomics research.

1. National policy on genetics and genomics research: It was encouraging to see reference to a focus on rare disease in the 2020 Programme for government which also proposed the establishment of a national genetics and genomics medicine network. The statement is welcome but there is little evidence of any true progress in the development of any genomics policy in Ireland and it needs to be much broader in scope than a focus on rare disease and consider both the clinical and research domains in complex diseases and oncology to be impactful.

2. Need for education and balanced dialogue: Critical to development of a vibrant genomics ecosystem is balanced and mature dialogue around the risks and benefits associated with genomics research. To realise the promise of truly personalised healthcare it is important that individual citizens in Ireland understand why healthcare data sharing is beneficial to the collective and understand fully the true risks they face when they participate in such research.

Complementing public education and awareness, we also believe there is a need for greater investment in professional skills development in areas such as clinical genetics, genomics and clinical research, bioinformatics, advanced statistical analysis including artificial intelligence, medical, privacy law and ethics.

Sustainable and targeted infrastructure investment: Ireland's geography, ancestral and migratory history, combine to create unique research opportunities to identify genetic variation that may be associated with health or disease. However, Ireland's research infrastructure particularly in the field of genomics is very weak. Particular initiatives that have the potential to be transformative would include;

- accelerated investment in the establishment of a nationally co-ordinated clinical genomics service,
- the establishment of a national biobank and health data storage infrastructure,
- the creation of a national genomics project,
- the acceleration of investment and development of a national ethics committee, and
- greater national investment in participation in European health research infrastructures such as BBMRI-ERIC, ECRIN-ERIC, EMBL and relevant initiatives such as the European "Beyond 1 million Genomes project".

Dr Avril Kennan

CEO Health Research Charities Ireland (HRCI)

Overcoming divisions to unlock genomics potential for patients

For the average patient affected by a health condition with a genetic element, their needs from genomics are pretty simple.
- Can my data be used to help me and others like me?
- Can I fully trust that my data will never be used against me or my family?

While the needs may be simple, in Ireland we unfortunately find ourselves in a position where many complicated barriers are converging to result in a failure to support and enable strong progress in genomics research. These barriers include a lack of national leadership and guidance, a lack of public investment, concerns over inappropriate use of patient data and limited patient and public involvement (PPI) in decision-making thus far.

As we invited submissions to this discussion paper, we encouraged the authors to bring their personal perspectives and stories to the pieces they were writing. Through the process of putting together this event we, in HRCI, gained a perspective of our own, on a less-acknowledged barrier to progress. It became clear to us that the discussion and debate around genomics in Ireland has become so divisive as to become a risk to progress. It can seem at times that in order to have a say on the future of genomics research, it is necessary to declare whether you are on the 'side' of private or public-led initiatives.

Like everything in life however, things are not so clear-cut. Commercial approaches are not inherently bad, and they can be a route to much-needed financial investment. However, private companies do need to be fully transparent about how patient data will be used and who will benefit from it. It is important that they are held to account on

these matters. They should also ensure that patients are receiving value from their generous donation. Such value for patients may be through the return of information to benefit their clinical care, through receiving some tangible and appropriate incentive in return for their data and/or through their data being made more widely available to the research community (with the presumption that the data will be carefully protected from misuse).

In terms of public investment, there is much potential for good to come of it but only if that investment actually happens. The State is not currently taking enough ownership in supporting genomics research and there is not yet enough political will to ensure progress in the near future. The mention of a National Genomics Medical Network in the current Programme for Government is a welcome inclusion. However, as anyone working in patient advocacy will tell you, such a mention is just a start and politicians will need to be encouraged and persistently reminded to act on their commitment. As has been suggested by others, in addition to the Department of Health, there may be a role for the Department of Further and Higher Education, Research, Innovation and Science to play in progressing genomics. The involvement of Sláintecare will also be essential.

A successful future in genomics for Ireland is likely to involve a mix of public and private investment. In order to make good decisions around how members of the public are recruited for studies and how their samples are used, on-going and frank discussions, that are inclusive of all perspectives, will be important. Most essential of all will be a very high level of PPI in all decision-making. In order to facilitate meaningful PPI in genomics research, it is important that the public understand the value of genomic data and that they do not lose trust that their data will be safeguarded. In HRCI we have therefore been advocating not just for increased public investment in genomics but also for a public health campaign highlighting the value of health data for research and explaining the importance of patient consent.[1] COVID has honed our national skills in public health messaging – let's also put those skills to use to benefit the future of genomics.

1. HRCI position paper 2019: Research Towards a Healthier Ireland. https://hrci.ie/

Prof Walter Kolch

Director, Systems Biology Ireland Director, Precision Oncology Ireland, School of Medicine, University College Dublin

Why and how should we advance genomics research in Ireland?

JAMA's history of medicine puts the sequencing of the human genome and the beginnings of personalised medicine side-by-side. Within 20 years genome sequencing advanced from an exotic and expensive research extravaganza to an affordable and precise clinical diagnostic tool. Single cell sequencing and the new gene editing tools around the CRISPR technologies suggest that the genomic tsunami continues. Not participating in this revolution is like throwing our Smartphones/iPhones away. Unfortunately, Ireland is doing exactly that.

Genome sequencing already has proven its value for improving diagnostics and therapy choices in any single medical discipline where deployed. Its impact on medicine rivals that of antibiotics and vaccinations. Emerging health economic studies show that it saves treatment costs, without even considering knock-on savings as better treatments mean less sick leave and faster return to work. Given the fast developments in genomics, both a strong research base and a clear strategy for implementation are needed to realise these benefits.

Ireland has a fragmented infrastructure for genomics research, which has pockets of research excellence but is largely ineffective in clinical applications. However, Ireland has many ingredients for cutting edge genomic research

(systems biology, data analytics, genetics, bioinformatics). Rallying these efforts under one umbrella can catapult Ireland to the forefront. However, it will need a top-down policy and funding model that addresses:

1. Regulation of genome sequencing for clinical and research purposes that includes the relationship between private and public entities active in the area. It also needs to address privacy and a more research-friendly interpretation of GDPR. The current Irish health research regulations are stifling research, both basic research and clinical research.
2. Setting up a national centre for genome sequencing. This should have a clinical and research arm and associated infrastructure for sequencing, analytics, and data storage. The coupling between research and clinical sequencing makes sense as there are still fast technological developments. For instance, single cell sequencing will become very important for assessing patients' immune responses to a tumour but is currently a research technique.
3. Introduction of genome sequencing into clinical practice. A feasible model would be a hub and spoke model. The hub would be the national genome centre doing whole genome sequencing, clinical validation of new methods and the associated analyses. The spokes would be gene panel sequencing in the clinical labs in the large hospitals. This will cover 50-70% of the clinical needs and is relatively cheap in terms of investment and does not require expert skills to run. At the interface one will need to set up disease specific molecular clinical boards, where genome experts and clinicians discuss the findings so that efficient clinical implementation is enabled.
4. A training and upskilling programme especially for clinical genome research
5. Funding pilot projects in areas where genome sequencing is known or expected to make a big impact, e.g. cancer. These projects will be valuable to (i) develop best pathways for implementation, and (ii) perform a health economic analysis of benefit and true costs of genome sequencing.
6. Includes future technologies for functional genome analysis, such as transcriptomics, proteomics, metabolomics, data integration and computational disease modelling. These technologies are following on the foot of genome sequencing and will help interpreting the genome information in health and disease.
7. Genomics is the prime example where basic research jumped straight into the clinic. Single cell analysis and CRISPR will do the same. Therefore, a competitive genomics infrastructure must combine research and clinical application. It also must accommodate the rapid advances in other omics technologies and data integration.

Prof Mark Lawler

Associate Pro-Vice-Chancellor and Professor of Digital Health, Queen's University Belfast

Integrating genomics and health data analytics into health care: an all-island priority

Over the next decade, genomic data from many millions of patients will be generated within healthcare globally. But are our health systems ready for this genomic medicine revolution? If not, they need to be. In the UK, Genomics England has now sequenced over 100,000 whole genomes and has deployed the intelligence gathered to help dissect the complexity of disease for the clinical benefit for patients. The recent announcement of an overarching genomics strategy for the UK, allied to the Accelerating Diagnosis of Disease programme, emphasises how genomics must be a critical part of our health system, informing how we best control disease and preserve human health. But where do we stand in relation to the integration of genomics into health care here in on the island of Ireland? Unfortunately, particularly in Ireland we are a long way behind, both from a genomic and a data perspective. Northern Ireland has benefitted from its association with Genomics England and the national focus on the role of genomics in delivering better health services. While a number of reports have emerged in Ireland on the importance of genomics and data to health care, they have yet to be implemented.

Allied to the technical development of genomics and data analytics, there is a clear imperative to share clinical, epidemiological and genomic data in order to enhance our understanding of disease and translate that knowledge to better health for our citizens. If there is one lesson that the COVID-19 pandemic has taught us is that there is an absolute need for timely accurate data in relation to our health and wellbeing to be made available rapidly and to be deployed effectively.

Beyond the technical requirements of establishing genomic and bioinformatics capacity, one of the key barriers to widespread clinical implementation is the need to ensure that clinical and genomic data can be brought together in a responsible and effective manner to enhance the health of population of this island. An all-island level initiative, presenting a unified voice to governments to inform future policy development and service planning would have merit. The framework developed by NHS England in conjunction with Genomics England to commission Whole Genome Analysis for routine care provides an example of integrating the clinical evidence base with operational and financial considerations to underpin better health.

Breaking down data silos to accelerate the production of evidence that directly improves patient outcomes is a key aspiration. An all-island Genomic Medicine programme, appropriately resourced and with a parallel education programme, would provide a unique opportunity to address many of the significant health challenges that we face within both of our health systems on this island.

We have a responsibility to the citizens of this island to accelerate the implementation of genomic medicine, allowing the benefits of genomics to be realised for individual patients, families and healthcare systems. We are at a crucial inflection point, where sustainable investment in genomic and data analytics infrastructure across this island will pay a significant “wellness” dividend, enhancing the health and well-being of our population and allowing innovation to flourish and deliver not only health, but also socioeconomic benefits. We need to grasp the opportunity.

Dr Sally Ann Lynch

Clinical Geneticist, CHI @ Temple street & Crumlin, National Rare Disease Office, MMUH

Pushing the boundaries whilst remaining safe, a delicate balancing act

There is no doubt that advancement in genomic science has allowed us make new diagnoses in patients with rare disease. We are moving towards a future where broad-spectrum medicines will be replaced by targeted therapies specific to an individual’s genomic make up reducing adverse drug reactions and improving efficacy of medications. There is a lot to be positive about.

As a clinical geneticist, my practice deals with the new diagnoses achievable through genomic technologies and the challenges we face therein. Whilst the technology increased the sensitivity in analysing DNA and improved the diagnostic yield, it also revealed the extent of human normal variation which took us by surprise. As it can be difficult to work out if a DNA variation is a normal finding or a disease causing one. This risks mis-interpretation of data leading to possible misdiagnosis or missed diagnoses. New American College of Medical Genetics guidelines were introduced in response to these concerns. Whilst these guidelines were needed, they are constantly evolving as they struggle in certain scenarios, particularly adult onset disorders.

One big mystery is what does the 98% of our DNA that is not active genes do, the so-called junk DNA? The yield from testing active genetic material (e.g. a trio exome test comprising 2% of our DNA) in a child with malformations and Intellectual disability is 40%, this only increases marginally when doing a trio genome - where all the DNA is analysed[1].

That begs the question, where are the missing diagnoses when the genome test is negative? The likelihood is that it's in the genome (but we're missing it) or in the way the genome is being processed. This is analogous to a light bulb not working. It is either the lightbulb itself (the DNA) or the switch (the processing). We are good at spotting most DNA changes but some, e.g. chromosomal rearrangements, can still be tricky to see. Currently, we analyse DNA in a very two-dimensional manner but humans are three-dimensional beings. Our chromosomes, structures made up of our DNA, don't behave as stick-like static configurations in our cells in real life. They curl around each other and are dynamic in nature; we have yet to develop good tools to understand this. Watch this space as research closes this knowledge gap.

What about the families?

The problem with genomic technology is that many clinicians who order the test struggle to interpret the report. Many families in clinic report that they have been told nothing about the significance or meaning of the test report done by the referring clinician. The clinician may tell them "something has been found and clinical genetics team will explain what it means". Indeed we will, but these families will worry whilst sitting on our very long waiting list, possibly just to be told, it's normal human variation. A Google search of any chromosomal/genetic finding will yield scary results, many families come with misinformation from searches they have done themselves. This is unlikely to change in the near future. Therefore, whilst the yield from genomic research is marvellous, the follow up is anything but. It is not fair to do a test on a patient and not explain the result. However, it is not fair and unrealistic to expect primary clinicians to understand complicated genetic test results. As these primary clinicians have to be the ones ordering the test, the gap in the support given by clinical geneticists to primary clinicians needs improving. Bottom line, we need to increase the number of specialists if we are to maximise benefits from genomic research.

[1]Wright CF et al. Paediatric genomics: diagnosing rare disease in children. Nat Rev Genet. 2018 May;19(5):253-268).

Mary Maguire

PHC Squad lead, Roche Products Ireland

Roche's vision for personalised healthcare

Our vision at Roche is one of personalised healthcare, a patient-centric approach in delivering real-time and sustainable healthcare. To achieve this, healthcare systems need to be able to provide fast access to the right types of healthcare interventions for all patients who need them. This type of healthcare delivery requires a continuous cycle of insight generation driven by data and technology allowing for deeper insights into disease, improved patient care plans and prompt access to interventions. The level of insight generation and health information available to us now is unprecedented. It is anticipated that over 2,300 exabytes of health data will be generated alone in 2020. This is the equivalent to 100 people browsing the web for over 100million years. A significant proportion of this healthcare data is coming from genomics and the abilities researchers and clinicians now have to understand a person's disease at the level of the genes. Genomics has the potential to transform the future of healthcare by offering patients the very best predictive, preventative and personalised care.

Importance of integrating genomics research and clinical care

True personalised healthcare can only be achieved at the interface between the laboratory and the clinic where real-time insights can be rapidly translated into better interventions for the patient. The advent of rapid genome sequencing allows us to update the promise of bench-to-bedside medicine to bench-to-bedside-to-bench medicine using a systems approach. Cancer therapeutics in particular can benefit greatly from this integration between the genomics lab and the clinic in a variety of different ways. Patients can now be selected faster for clinical trials based on genetic biomarkers. Broad profiling of a patient's cancer allows a variety of druggable targets to be identified using only one diagnostic procedure. Liquid biopsies now allow for minimally invasive ways to access this genomic information for patients. Patients can now be treated for their cancer based upon their genomic profile regardless of where the tumour is in the body. Interval genomic profiling of a cancer patient throughout their illness can monitor for the appearance of resistance mutations allowing patients to switch through several lines of treatment. This gives us the potential of cancer becoming a chronic, and not terminal, diagnosis. Prior to 2014 patients diagnosed with a lung cancer driven by an ALK mutation in their DNA were given a prognosis of months to live. Since then, 5 new medicines are now available focused specifically on this genetic mutation, 3 of which can be used consecutively as resistance mutations arise. This has extended survival for these patients from months to beyond 3 years. This was all developed within a 6-year timeframe. Genomics has unleashed a remarkable wealth of information for patients and importantly, the technology is available to translate this information into actionable insights for patients, personalising their care.

Prof David McConnell

Fellow Emeritus in Genetics, Smurfit Institute of Genetics, Trinity College Dublin

Genomic medicine: for whom and how?

Genomics, the study of whole [or large parts of] genomes, is one of the most powerful new methods for investigating, explaining and developing diagnostics and therapies for any disorder with a genetic origin. Based on high quality clinical diagnostics and medical records, high throughput Whole Genome DNA Sequencing (WGS), and complex data analysis, it is being used to study and treat single gene and multifactorial disorders [cancer, heart disease etc. etc.] with great success worldwide. Many genes are being discovered in which variation predisposes to illness, and it is now becoming routine to use genomics to search for such damaging genes in patients [and their relatives], helping to decide on treatment and counselling. Ireland, with its poor record in medical genetics, has not invested significantly in medical genomics with the result that initiatives by researchers have led the way. Fighting Blindness has helped to fund WGS to identify Retinitis Pigmentosa in 1000 Irish patients and their families. Irish clinicians treating patients with Motor Neurone Disease are taking part in the crowd-funded international Project MinE WGS programmes. Some WGS seem to be funded for commercial objectives, and these are posing serious challenges for researchers, clinicians, hospitals and universities.

The overall result is that very few Irish patients are benefiting from advances in genomics. Moreover, there are serious concerns that patient clinical records may not be secure. We need a clear national policy in genomics. Let me lay out some objectives to allow us to get things right.

I am alarmed by the role of private genomics companies, for example GMI/Genuity Science, in Irish medical research [see McConnell and Hardiman, Irish Times 3rd July 2019] who are seeking access to medical records and tissue samples for DNA sequencing and analysis. I can supply copies of this article which laid out four guiding principles:

1. The primary objective of genomic medicine is to enhance patient care within the public health system.

2. Doctors, scientists, hospitals and research institutions must be educated and funded in preparation for the important advances in genomic medicine.
3. Since the field is so new, there should be a strong focus on high-quality genomic research by clinicians and research scientists.
4. And finally, it is very important that genomic research work should be shared internationally. This allows medical researchers to collaborate with each other and with pharmaceutical partners who are engaged in new gene-based therapies.

In order to achieve these objectives, there should be a National Genomics Policy and Programme controlled and substantially funded by the Government to develop research and clinical treatment. Clinical genomics must become part of Irish medical practice, to be led by consultants and scientists. This will require major investment in clinical and laboratory services, close coordination between clinicians and scientists, and between hospitals and universities. Moreover, a national genomics programme must have the support and approval of the public, guided by patient and family interest groups.

The clinical records of our patients should of course remain confidential. They are priceless assets, collected over decades, mostly at public expense, for the benefit of patients. They are also invaluable for the development of new diagnostics and treatments and can be made available for bona fide research. Genomics medicine research requires the pooling of medical records which must be professionally and confidentially curated by the researchers. I am concerned that such records should not be handed over to any commercial organisation except under very strict rules which protect the interests of the patients, their consultants and scientific advisors, and the responsible public institutions.

I hope that this conference will refine and confirm these principles so that Irish genomics research and medicine, funded by the Government, charitable foundations, sometimes in well-regulated partnerships with commercial companies, can be focussed on patient care.

Dr Verena Murphy and Eibhlin Mulroe

Head of Research and CEO, Cancer Trials Ireland

The importance of integrating genomics research into cancer clinical care

Technical advances in DNA sequencing and computational biology in the last two decades make it possible now to analyse the entire genome of an organism. This became very popular in conjunction with the ancestry research and a large number of companies started offering whole genome sequencing on a commercial basis. Whole genome analysis (WGA) became very important as part of precision medicine. It allows to search for the origins and reasons for many diseases including cancer and has become a regular tool for research in many laboratories all over the world. Ten years ago, cancers were characterised by their cell appearance and the origin where they manifested themselves first, e.g. cancer of the lung was classified as small cell or non-small cell lung cancer. WGA allows a much more detailed analysis of the genomic make-up of the tumour and can provide insights into how an individual's cancer might progress, and its likely response to treatment. The addition of WGA in the process of a cancer diagnosis has started shedding light particularly into the genetic make-up of less known/rare types of cancer and opened up new treatment opportunities. While in some cases WGA can save the life of a cancer patient in other cases it produces valuable data, which might not help the current patient; however, offers targets for new drug development.

In 2010, Jones et al. were the first to publish an example of clinical treatment decision-making based on whole-genome analysis (WGA) of an adenocarcinoma of the tongue, a rare salivary gland tumour (2010, Genome Biol.). The treatment of the primary tumour and later the metastases was based on WGA and was able to slow down progression by several months. A study by Laskin et al. (2015 Cold Spring Harb. Mol. Case Study) could demonstrate the usefulness of the integration of WGA in the care of late stage cancer patients. In 55 out of 78 patients WGA resulted in actionable data and 25 out of these 55 patients received treatment based on the WGA results. However, a multidisciplinary team of clinicians and scientists is needed to implement WGA into the care of cancer patients to inform systemic therapy decisions.

In Ireland, the current standard of care does not include WGA, and is based on the analysis of known molecular markers to help guide the most suitable targeted treatment. Many cancer centres worldwide have been experimenting with targeted “panel” sequencing of selected mutations and further advances in the genomic technology enable the generation of genome-scale data sets for individual patients. However, this carries a risk of missing meaningful somatic alterations. Pathology departments in larger hospitals are now equipped to perform WGA on individual patient samples; however, only selected countries include WGA in the standard of care. Private companies have been established within the last 5 years, who offer WGA as a service on a commercial basis. However, an important aspect in offering WGA as part of the clinical diagnosis process is that the results of the analysis will be conveyed by the treating physician and discussed with the patient. Without the knowledge how to ‘read’ the results these data can either be useless for the patient or completely overwhelming causing anxiety and uncertainty.

There is a need for the integration of WGA in the standard cancer diagnosis process for the difficult-to-treat cancer types, e.g. pancreatic cancer, and for advanced cancer stages, e.g. metastasising cancers, where treatment options are limited or non-existent. For some patients, the information gained from WGA can save their life; in other cases, it adds new data for potential discoveries to help future patients.

Cancer Trials would welcome

- Guidelines on conducting genomic research,
- One nationally-funded entity to receive control samples to build a publicly available library,
- A regulatory agency providing oversight of all entities in Ireland conducting such research, and
- The involvement of the patient in the decision making around all of the above.

Dr Robert O’Connor

Director of Research, Irish Cancer Society

Genomics - managing a modern Pandora's box

The year is 2040.
You apply for a mortgage but it seems very costly compared to a friend applying for a similar house loan. Further investigation reveals that the Artificial Intelligence reviewing your application has integrated a loading based on a mathematical guess that you have a short life expectancy. Further investigation unearths that the genomic data used by the AI came from a routine blood test undertaken by your mother in 2020.

How do you feel about this?
Far-fetched “science fiction”?

Perhaps but every individual element necessary for this story has already occurred and while there are variable legal protections depending on jurisdiction, there is no technological impediment to it happening now. For example, a mass murderer was recently identified by interrogation of genomic information harvested from members of the public giving samples just to identify their ancestral origin[1].

Genomic information is a modern Pandora's box, holding a promise of contributing to better understanding and treatment of disease but, in the wrong hands, potentially impacting not just our own lives but those of our descendants.

The order and arrangement of four simple bases, albeit vast stretches of those bases collected into complex genes and chromosomes, instructs the basic behaviours of our cells. Many devastating diseases have at least part of their origin in the arrangement/disarrangement of those sequences. Hence, understanding of the correlation of those sequences with factors such as disease holds the potential (but not a guarantee) to identify causes and treatments of some diseases. Dissecting these links requires vast amounts of information (genetic, health and personal) both from the individual and from large numbers of other individuals but the utility of those correlations is only as good as the technology, integrity and expertise behind the analysis. Turned on its head though, analysis of an individual's sequence can also be used to extrapolate other health characteristics with potential serious health or financial consequences. Few of us can truly understand the fundamentals of the technology and its limitations nor its implications and ramifications hence we can only contribute in an informed way if we can truly trust the context of the analysis. For example, genomic analyses routinely employ pseudoanonymised/de-identified information – (information with the name and some other details removed). However, by employing complex analyses, a small number of pieces of sequence information can be used to reidentify a participant[2].

One might therefore imagine that repositories of genomic information are in some ways akin to banking in that the system only survives while its investors (those contributing their DNA) have full confidence in the integrity of the system as a whole. Poor security/management will lead to loss for the individual and potentially all of their descendants. Poor confidence will stop individuals investing in the first place, undermining the potential promise of this technology as a whole.

So how can we progress and manage this new biological Pandora's box?
Taking these points together suggest to me that three key elements are critical for future progress:

1. we need a well-supported ethical and regulatory framework which has the expertise, authority and power to protect stakeholders and where individuals can be independently confident that their data is ironclad safeguarded, especially against the backdrop of easy instantaneous global transfer of information through jurisdictions with very different perspectives on privacy. Without trust we risk not getting the "investment" we need from the public and individuals, and their descendants risk great loss.
2. We need to invest in understanding for our public, its representatives and those who might handle such information to ensure a shared set of values and context
3. The exploitation of genomic information has to prioritise community and the person over commercial interests. The technology and skills required are expensive but commercial interests must serve rather than drive the agenda.

I contend that our nation needs to invest in these three areas lest my "science fiction" become day-to-day reality.

[1] https://www.sciencemag.org/news/2018/10/we-will-find-you-dna-search-used-nab-golden-state-killer-can-home-about-60-white

[2] Lee SW. Ethical Implications of Clinical Genomic Information, Records Research, and Informed Consent. *Ochsner J*. 2018;18(3):196-198. doi:10.31486/toj.18.0052

Prof Pat O'Mahony

Chair of HIQA and IMVO, former CEO of CRDI and HPRA

Genomics - time for a senior cross-departmental lead

I welcome the opportunity to provide a short contribution to this important topic of Advancing Genomics Research in Ireland for discussion at the Irish Health Research Forum (IHRF), as ably managed by Health Research Charities Ireland.

I will begin by commenting on the broader topic of clinical research. I draw the readers' attention to the report on the Future Investment in Clinical Research published by Clinical Research Development Ireland (CRDI) in May 2019. This report sets out a clear and well-supported case for the benefits that a well-developed clinical research infrastructure and activity level bring for all stakeholders, citing the significant advantages for patients in such a scenario and for economic growth impacting on the research community and industry sectors. The report also outlines in broad and high-level terms the steps required to advance from the present state to a brighter future where clinical research is enabled and integrated into the healthcare delivery system. The content of the CRDI report and all the recommendations therein apply equally to research in genomics.

The 2019 CRDI report calls for the appointment of a senior strategy lead at cross-departmental level with a well-funded support office. Under the Programme for Government 2020, we now have the establishment of a new Government Department for Higher Education, Research, Innovation and Science. This Department should now take the lead role in urgently drafting a policy for Genomics Research and establish a clear strategy for its delivery.
The CRDI report calls for the establishment and funding of 1) a national coordinating entity, and 2) an office at HSE/Service Delivery Level to coordinate all aspects of clinical research, and for the application of the additional Exchequer and Industry co-funding proposed in the report. This certainly applies in the field of genomics research. This office is in place and the head of the office needs to be at National Director level. The HSE has also planned for a clinical lead for genomics and this position should be filled without delay. Specifically on the topic of co-funding, I fully support the concept of deep coordination and collaboration between public and private entities engaged in genomics research. In fact, at present we have relatively small public investment but significant private sector investment in genomics research in Ireland. The potential benefits are significant and, while understanding a viewpoint that might favour a public investment model, it is in my view imperative we harness the opportunity presented by private investment and leverage this now in a very major way.

The CRDI Report calls for significant changes and enhancements to the clinical research system and the healthcare delivery system and in the field of genomics research these include areas such as the overall legislative and regulatory framework, ethics approval, real coordination and resourcing of national biobanking resources, and an enabling, proportionate and supportive data handling system and processes.

Finally, as in all areas of healthcare, every person and stakeholder involved needs to maintain an absolute focus on the patients we serve. We need to enhance and support patient involvement in genomics research and all we do should centre on what is best for patients. We need to listen to patients, carers and families. We need to "make it personal" to what enhanced genomics research can bring for individual patients and for society, and for the improved clinical care and enhanced personal decision-making genomics research can enable.

We should of course build on the many existing national and international links already in place on Genomics Research and harness the power of these collaborations.

I thank the IHRF and Health Research Charities Ireland for raising this important topic at this time and I hope the discussion at the Forum leads to real and meaningful progress.

Prof Oran Rigby

FCICM FJFICMI. President Akkure Genomics

Next generation precision virtual trial networks

Clinical research is the foundation for innovation that can impact patients. Patients themselves are at the centre of the research equation; their medical profile and history are aggregated, analysed, and curated to understand diseases and make new discoveries. Recent trends in this field have involved advertising aimed at enticing consumers to give up their genetic data to 3rd parties under the guise of Genealogy, with subsequent exploitation of this data to interested commercial parties. We must take the opposite approach, a patient first approach which allows patients leverage their own health data (fusion of clinical with genetic and biometric/physiological parameters) based on a networked community (virtual) of national and international patient groups.

Data is the new gold. A Stanford University School of Medicine Report estimates that next year 2,314 exabytes (1 exabyte = 1 billion Gigabytes) of health data will be produced, indicating a 48% annual increase. The incredible field of precision (genomic) medicine is approaching at breakneck speed. Precision medicine is set to transform the clinical trial industry. This next generation of clinical trials requires fast, comprehensive and cost-effective genomic profiling of patients themselves. There is an understandable reluctance, fear and indeed suspicion of sharing highly personal information. Yet ignorance is not protection, whilst knowledge is power. Collective knowledge empowers change and influences future research and cures. Individual and isolated medical data has minimal to no value. Its value lies in sharing and contributing individual data from a cohort of similar conditions, allowing insights and thus information to be derived. This is the underlying concept of Big Data, neural networks and subsequently AI. It is also a fundamental principle of applied medical research.

Critical to this new shared patient research paradigm is the concept of ‘selfish altruism’, whereby an individual’s contributions help both them personally yet also assists thousands if not millions of others suffering from similar illnesses. However, the benefits are not confined to a point in time. The benefit is dynamic, hyper-personalised and evolves over a lifetime. Fusing machine learning with big patient data in the form of cohorted genotyping will facilitate new insights into DNA ‘dark matter’ and recognition of patterns or bundles of genes that may be associated with specific disease. Therefore, the more people sharing, the more powerful the benefit becomes to each individual personally. A genuine and powerful aligned incentive for all.

Thus a network is required for sharing, contributing and connecting. This pooled, connected and filtered data becomes a tremendously valuable resource for healthcare and patient communities. This data can be converted to information and subsequently utilised in interventions aimed at optimising healthcare, known as therapeutics, (pharmaceutical, lifestyle, surgical etc). Therefore, any entity seeking to develop new therapeutics or establish feedback on existing therapeutics needs a targeted subject cohort relevant to their area of intervention. This is where Virtual Trials, precision trials and networked data become mutually intertwined and synergistic.

Collection and analysis of identified genomic samples should be linked with matched clinical data from electronic health records and subsequently validated with relevant physicians. This combination is vital to connect genes with disease and therapeutics. These digital fingerprints would allow patients to own, share and monetise their health data and make it available for research (virtual trials). Patients would have very granular control over what part of

their EMR could be accessed by whom, many decisions could be automated into smart contracts resulting in instant reward if certain trial conditions are met. The alternative is a lifetime of drug 'mortgages' for patients, with new powerful, personalised drugs unaffordable without decades of repayments.

In return for allowing access to their data a patient could receive shares which they could use as payment for future healthcare services, ownership of the network, fractional ownership of rights to the end therapeutic/drug developed as a result of the trial or possibly even exchange for fiat currency. Ideally this reward would be collectivised and brokered to ensure leverage of patient power. Monetisation and revenue is directed away from large pharmaceutical corporations and their contractors and back to the doctors and patients, transferring and capturing the value of clinical trials to those creating, owning, and validating the health data. This mechanism incentivises patients to partake in creating personal EMRs and capturing their outcome data, rewarding them both directly and indirectly for participation. This is true patient centric care, incorporating control, ownership, reward and involvement at the heart of the health continuum.

Prof Cathal Seoighe

NUI Galway

Maximising the benefits of genomics – why it's a matter of time

Genomics can help in the search for new treatments for human diseases. Comparing the genomes of affected and unaffected people often opens a path to new ways of thinking about treatment. There has been particularly good progress in cancer treatment because cancer usually starts with a DNA mutation and the effects of the mutation can be targeted by drugs. While scientists working in universities and research institutes often derive insights that help identify new therapies and sometimes find new candidate drugs, the drugs are usually developed and tested by large pharmaceutical companies. This is because of the high costs involved. Much of this cost is due to the many drug candidates that fail in clinical trials. This waste can be reduced through genomics, with pharma companies reporting that drug candidates selected with the help of genomics are much more likely to succeed.

Pharma companies are eager to access genome sequences to reduce drug development costs. They often access these data as clients of specialist genomics companies, or by participating in public-private partnerships. In one recent example, four major pharma companies teamed up with the UK government to sequence the genomes of 500,000 people in the UK. The sums of money involved are large – the pharma companies will contribute around £100 million. In return for this investment, they will get exclusive access to the data for two nine-month periods (after completion of two phases of the project) before the data is made more widely available to the research community.

The short time of exclusive access is why this is a good deal for the UK public. In principle, a pharma company that has exclusive access to genomic data indefinitely could 'sit on it', secure in the knowledge that other companies cannot gain a competitive advantage from the data. With short periods, the companies must work quickly. However, pharma companies are not simply concerned with gaining a competitive advantage. Companies are willing to work together because everyone benefits by reducing the waste resulting from drug candidates that fail clinical trials (no one more so than clinical trial participants). Short exclusivity periods also ensure that the data are made available to the wider research community as early as possible, leading to new scientific insights and suggesting yet more promising directions for treatment.

What does it mean to own something? Fundamentally, it is about time. You own something if your possession of it has no meaningful time limit. A one hundred year lease on a building is quite like owning it. In the example above,

the companies do not own the genomics data. Their exclusive access is time-limited. In a sense, the data has been lent to them by the UK public, in exchange for funding the data generation.

What can Ireland learn from this and other similar examples? The enormous value of the UK Biobank derives from the people who have agreed to participate in it and the publicly-funded effort that has gone into participant recruitment and collection of clinical information. In Ireland, we do not have a comparable cohort, but we do have some interesting sample collections that are relevant to specific diseases. These sample collections have been established through public funding and the goodwill of Irish patients. The state has a key role to play in overseeing access to these collections in a way that ensures patient rights are protected and facilitates constructive partnerships with the private sector. This should embody the principle that the data always belongs to individual patients and restrictive access to collections of genomics data should not be maintained indefinitely. Population-scale genomics data sets should not belong to private companies and that means that exclusive access must be time-limited. These time limits should be kept as short as possible, to maximize the benefits to the broader public, but remain long enough to incentivize private investment that will help unlock the benefits of genomics for Ireland.

Prof Owen Patrick Smith

CBE, Hon FTCD. Academic Lead, Children's Health Ireland, Consultant Paediatric Haematologist, Children's Health Ireland at Crumlin, Dublin, Professor of Paediatric and Adolescent Medicine, University College Dublin, Hon. Regius Professor of Physic [1637], Trinity College Dublin, National Clinical Lead for Children, Adolescent and Young Adult Cancers, NCCP

Delivering paediatric genomic/precision medicine through Sláintecare

The primary mission of Children's Health Ireland is to ensure that the children of Ireland are provided with a level of healthcare that meets international best practice. Above all, it must offer highly developed tertiary and quaternary services across a broad range of sub-specialities, so that children with, life-threatening and complex chronic medical and surgical conditions can have the best possible therapeutic interventions that will deliver best clinical outcomes. Such excellence in modern paediatric clinical practice cannot be provided except in the context of discovery-focused translational research.

Over the last decade the landscape of paediatric health and wellbeing is being transformed through developments in the basic and clinical sciences, especially genomics and molecular biology. As a result we are now witnessing the rapid arrival of a new era of child and adolescent healthcare. We are now beginning to see healthcare shift from a curative paradigm, where the emphasis was on managing disease, to a pre-emptive paradigm, where the emphasis is on predicting and pre-empting disease using genomic information and molecular technologies. For example, it is now possible to identify an individual's genetic inheritance and the molecular biological basis of disease which in turn greatly facilitates the personalisation of medical care by predicting the disease predisposition of individual patients, tailoring medical treatment to these predispositions, and customizing disease management to achieve optimum medical outcomes. This new paradigm will in time will reduce the burden of disease, as well as well as the personal and societal costs of healthcare, by detecting and treating disease at earlier stages and pre-empting more serious consequences.

Pivotal to the realisation of this new paradigm will be the development of an electronic healthcare record (EHR) platform that will/should include consent (GDPR compliant) to undertake precision medicine translational research with an opt-out consent system that will be required if the power of genomic medicine is to be realised. Also, natural

language processing of EHRs to nominate patients for cohort studies to understand the prevalence of genomic variation in various human disease states and to provide disease reclassification (taxonomy) will become the norm. In terms of clinical research, the health informatics revolution will have a dramatic positive effect on how we will deliver healthcare into the future. Not only will the patterns of care change radically but also a rebalancing of role of, paediatricians, general practitioners, nurses, paramedics and pharmacists and other healthcare professionals will occur. Again, critical to this paradigm shift in healthcare delivery with be the development of a robust EHR as it will pull together the disparate fragments of the patient's diagnosis and treatment into an integrated healthcare information package. So, a significant amount of primary care that is delivered by general practitioners / community paediatricians will come from other healthcare professionals, equipped with secure access to the patient's record and recommended pathways for diagnosis and treatment. Therefore, it will be essential to train and equip all medical, nursing and allied healthcare professionals for this new expanded role in the future of care. The ultimate aim will be that the right patient receives, the right treatment, at the right time and in the right setting - **essentially this is far more logical and more cost effective.**

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Irish national genomic initiative and an accompanying national informed consent process

As a young UCG graduate, my first job working at the University of Utah was focused on running gene sequencing technologies for a pilot project to develop faster ways to support the then first human genome sequence. Subsequently, the first publication was an open-source initiative, published online, free and available to all[1]. Before then, the default of open-access data-sharing policies had been driven by the genomics community themselves, outlined in the "Bermuda Principles"[2] and guided by research scientists across the world. In the introduction to the human genome published in Nature in February 2001[3], the first article, entitled "Everyone's genome", reported that, "one principle at the heart of the Human Genome Project, reflected in the Universal Declaration on the Human Genome and Human Rights, is free and unlimited access to the sequence". To deliver this promise, there should be no controversy for the Irish government to launch the proposed national genomic initiative. What is controversial is that we have not yet started it.

Similar models of other national genomic initiatives are well established, publicly funded, professionally run, protected by and for patients, and routinely managed across the National Institutes of Health (NIH) in the US, at Genome Canada, at Genomics England and further afield, including Estonia (population of 1.3M) and Denmark (population of 5.8M). From a recent count, there are 18 currently active government-funded national genomic projects running globally. It would be fitting to celebrate the 20th anniversary of this Nature achievement with the establishment of the Irish national genome project next Spring, in February 2021. I find no reason for the conference not to support this initiative and deliver this critical objective for all patients.

Genomics should be built on the same open-access and free data-sharing policy as many international genomic programs. In the context of participating in clinical research, every patient is a very relevant stakeholder and if a national genomics initiative is to work, then the most important document at the centre of this process should be a national "informed consent form" (ICF) and process. Ideally, the proposed national informed consent form, and its accompanying patient information leaflet (PIL), will provide a legal document, embedded in EU legislation and under-pinned by the ICH-GCP[4]. Any patient participating either in a proposed national genomic initiative, or any

public or academic or commercial genomic initiative, will need to have the minimum protections of a clear set of non-negotiable consent forms, standardised, pre-approved and to be under-written by Irish legislation.

If accepted, genomic information may be warehoused under personal data protection legislation, following which, both academic and commercial organisations should be free to compete and develop new tools for diagnostic and therapeutic opportunities. Creativity will potentiate benefits for all patients. This approach is not unique. In the past decade, several controlled-access data policy models have been used to share data from thousands of genomic research studies around the world[5]. As of October 2018, NIH has provided over 5,600 investigators access to 1,025 studies, resulting in over 2,460 peer-reviewed publications contributing significant advances to a wide range of fields[6].

What are we waiting for?

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For further information

For further information on the activities of the IHRF please see our website: https://hrci.ie/ihrf/

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