


Making progress with newborn screening

Report from an event held in conjunction with  Cambridge Prisms
Precision Medicine

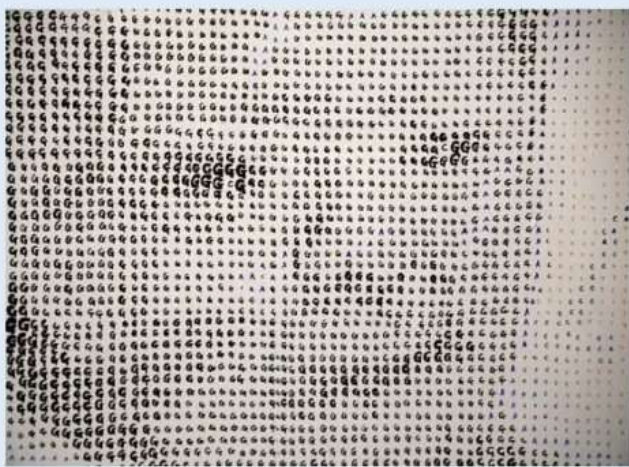
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We explored some of the challenges around balancing the benefits of extending screening for babies with rare conditions, with the involvement this requires from babies who do not stand to personally benefit, at a CPM event in 2025.

In line with the CPM's mission to '*support the development of equitable and effective personalised medicine; identify appropriate questions; facilitate constructive debate; and develop solutions across disciplines and audiences*', we aimed to create a forum for constructive and pragmatic discussion. This involved looking at where things currently stand with newborn screening, and considering how we can make the most of current research opportunities to test and improve the screening process.



CPM Youth Art Competition 2023-24

First place: Laranya, aged 13 from Worksop College, Nottinghamshire

The event brought together a range of people with expertise on different aspects of newborn screening, including representation from clinical genetics, metabolic medicine, obstetrics, neonatology, primary care, health economics, ethics, sociology, the National Screening Committee, the Generation Study, and the Oxford BRC patient and public involvement group.

We focussed talks and discussions around three historically contentious areas, aiming to find common ground and consider potential strategies to mitigate or navigate these challenges:

1. What would success look like in the context of a rare disease screening programme?
2. Navigating new uncertainties
3. Opportunities and questions raised by screening using genomes as opposed to more targeted options

This report from the CPM team summarises the talks we heard on the day, key points that arose from the panel discussions, and concludes with some thoughts around common ground identified, and opportunities and challenges arising.

The art featured throughout this report was created by young people aged 11-14 for the 2023-24 Centre for Personalised Medicine Youth Art Competition, on the theme of screening newborn babies for disease. Visual minutes were created by Zuhura Plummer. Image featured on the front cover is an excerpt from an artwork by Alexa, 14, Worksop College, Nottinghamshire.



Runner-up: Scarlett, aged 12 from Worksop College, Nottinghamshire

Where speakers gave permission, talks from the day can be accessed via our website:
<https://cpm.ox.ac.uk/watch-our-lectures-interviews/making-progress-with-newborn-screening/>

Event planned and report written by Rachel Horton and Anneke Lucassen, with support from Susie Weller and Sally Sansom. We are very grateful to Catherine Lidbetter and Thea Perry for their support with organising the event.

Please contact cpm@well.ox.ac.uk with any comments or queries.

Focus 1: what would success look like in the context of a rare disease screening programme?

Our first session, chaired by **Professor Anneke Lucassen**, looked at qualities of successful screening programmes, and considered how principles around screening should account for very rare conditions, where we do not have, nor can we expect to have, a wealth of data to guide decisions.

How to make good public policy screening recommendations for rare diseases: benefits, harms, opportunity costs

Professor Anne Mackie, Director of Screening, Public Health England

Anne spoke about the importance of population screening decisions being based on strong evidence, outlining how essential it is that research projects into new screening options collect data such that in time they can demonstrate the merits (or not) of a potential screening test. She discussed how the benefits of screening must be balanced against harms such as false positives, false negatives, uncertain results, diagnosis of indolent disease, and opportunity costs. Anne also discussed the challenge of supporting consent decisions around screening programmes in contexts where evidence is weaker, reflecting that some people might feel that they should participate in any screening offered in an NHS context.



Highly commended: Ahona, aged 13 from Francis Holland School, London

Do the current screening criteria in the UK set very rare diseases up to fail?

Nick Meade, Director of Policy, Genetic Alliance UK

We then heard from Nick, who set out discrepancies between the number of conditions screened for in the UK, and many other countries in the Global North. Nick discussed the challenges very rare conditions face in meeting stringent criteria for inclusion in screening programmes, using examples to illustrate how it is often not possible to collect extensive data regarding natural history and treatment response in the context of very rare, often only recently described conditions. Nick described how many families living with rare conditions wished that their child had been diagnosed earlier, and how some children had missed out on treatment opportunities because of later diagnosis. He discussed the hope of these families that expanding newborn screening might achieve earlier diagnosis and better outcomes for other children.

Principles for including conditions in the Generation Study

Dr Ellen Thomas, Chief Medical Officer, Genomics England

Ellen described how conditions have been selected for screening via the Generation Study. The study is motivated by how useful it would be if we could accurately diagnose treatable rare conditions earlier. Ellen discussed gaps in knowing how well genomics can identify rare disease patients from a healthy group and how the Generation Study hopes to generate evidence in this area. She explained how the Generation Study team made the decision to focus on genes and variants where we currently have the most



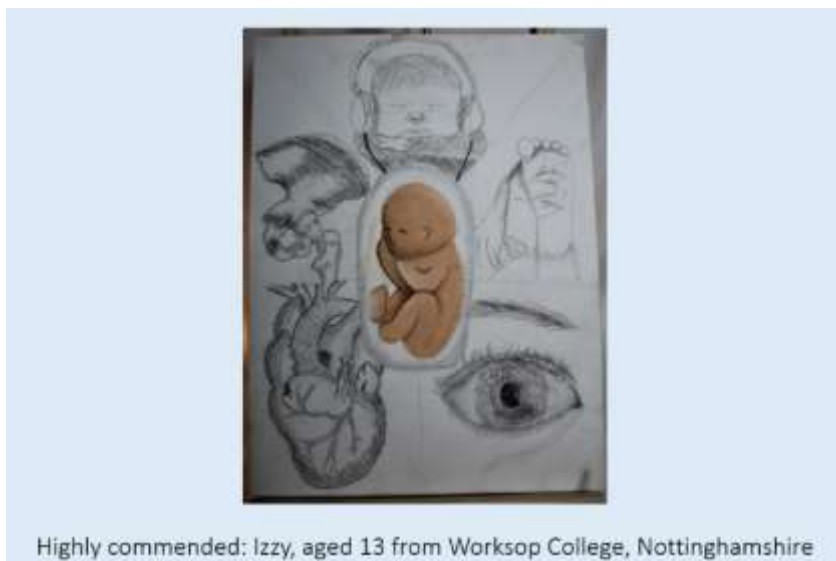
Highly commended: Alexa, aged 14 from Worksop College, Nottinghamshire

confidence in our ability to interpret and respond to positive findings. She outlined the principles by which these decisions were made, focusing on well-evidenced variants thought to be highly penetrant, and where early intervention has been shown to lead to better outcomes.

Building a health economic case for extending newborn screening

Dr James Buchanan, Senior Lecturer, Health Economics and Policy Research Unit, Queen Mary University of London

James discussed the current health economic evidence base for newborn screening, and what evidence might be needed to inform conclusions regarding its cost effectiveness. He started with the reminder that every spending decision in the NHS has an opportunity cost, and we need to collect evidence to determine whether using genome sequencing for newborn screening is justified given this will draw on funding that cannot then be used in other areas of healthcare. James discussed the challenges of generating health economics evidence for extremely



rare diseases, and how the Generation Study is seeking to combat this by evaluating broad condition groups rather than taking a condition-by-condition approach, evaluating cost-effectiveness for condition groups as a whole rather than at the level of individual disorders. He outlined the paucity of instruments for measuring health outcomes in newborns and laid out the importance of international collaboration in collecting and sharing relevant data, and using compatible methods, to develop evidence regarding which conditions should ultimately be screened for in the newborn period.

These talks were followed by a panel discussion in which the speakers were also joined by **Professor Sian Taylor-Phillips, Professor of Population Health, University of Warwick**. The starting point for discussions was the question: '*how should screening recommendations take account of rare disease?*' Key points arising included:

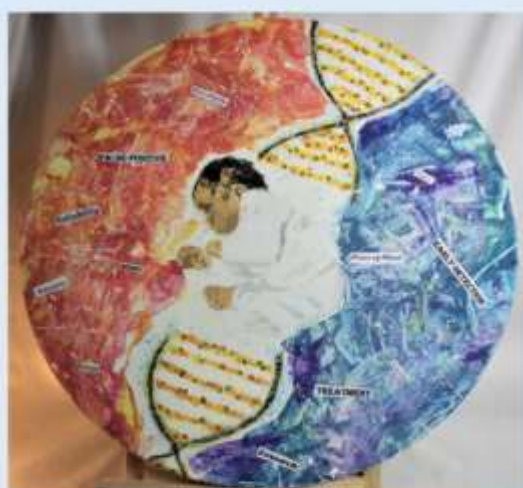
Strong recognition of the need to develop the evidence base around screening for rare conditions

- The panel discussed how **understanding the penetrance of particular genetic variants in a general population will be critical to developing a helpful screening programme** based around genomics. It was recognised that our understanding is currently skewed because many variants thought to have a high penetrance have primarily been studied in individuals tested because they were already symptomatic. The panel reflected on tensions arising from this issue: in communicating that a baby has a rare genetic variant that we think might lead to disease, might we lose the opportunity to truly measure penetrance, and commit ourselves to lingering uncertainty regarding whether screening is helpful? Yet if we wait for 'perfect answers', what might that cost in terms of babies who might miss out on early diagnosis and treatment?
- Discussion included **the importance of detailed, long-term follow-up for participating babies** in order to support our ability to learn as much as possible about how to improve newborn screening for future generations. There was widespread **agreement on the need for international collaboration**, as many countries grapple with which conditions to include for newborn screening, representing an opportunity to collect data on the scale needed to answer pressing questions as to which screening is on balance beneficial.

- The **value of resources such as old Guthrie cards** in generating data that could reduce some uncertainties around the penetrance of particular genetic variants was highlighted, though the panel reflected that such resources would need to be coupled with details around outcomes for the babies (now adults) who samples came from, and there would be significant complexities regarding what consent conversations might need to happen around such a study.

Challenges in supporting parents to make decisions around participating in screening *research* in the context of widespread deterministic narratives around genomics

- The panel considered **whether families are likely to be prepared for uncertainties that might arise from testing** such as that provided by the Generation Study. Looking to the future, the panel also reflected that **where screening is offered via the NHS, some parents may think it implicit that they should agree to their baby having this screening**, potentially undermining the extent to which they are likely to weigh up pros and cons of participation.
- Generation Study materials have been created with these issues very much in mind, aiming to make it very clear to parents that results may not be clear cut. The panel and audience reflected that even with carefully crafted materials to support parents to anticipate the potential for uncertainty, **challenges may arise given the context of prevailing deterministic discourses around genomics**. For example, it was raised that in surveys of families who had received a variant of uncertain significance from genetic testing of an unwell child, less than 20% had been aware of this possibility in advance of receiving the result (although this would routinely be mentioned as part of consent conversations for such testing).
- We reflected how one way in which the Generation Study is accounting for this issue is by trying to minimise uncertainty by setting stringent thresholds for a 'positive screen'. This means that **for many conditions we should expect its sensitivity to be low**. While much research will focus around tracking outcomes for babies who screen positive, and the consequences this has for families and the NHS, data will be collected for all participating babies such that over time we could model how particular genetic variants not reported in the course of the project might affect health in early years (and so generate evidence to inform whether they should be included in future screening programmes).



Highly commended: Lucas, aged 12 from Worksop College, Nottinghamshire



Focus 2: navigating new uncertainties

This session, chaired by **Dr Susie Weller**, discussed the challenges of interpreting genomic variation in a screening context, the challenges for families and clinicians of managing uncertainty, and the challenges of living with a rare condition.

The scientific challenge of predicting phenotype from genotype

Professor Caroline Wright, Clinical and Biomedical Sciences, University of Exeter

Caroline started the session with a talk that illustrated the challenges in using genomic data for prediction as opposed to diagnosis. She discussed the 'inconvenient truth' of non-penetrance, variable expressivity, and pleiotropy which make it very difficult to draw firm conclusions as to how a genotype might affect a baby's health, illustrating this with striking examples from her work with UK Biobank data.

Caroline also shared data emphasising the importance of expert curation of any variants considered for inclusion in a newborn screening test, showing that although this curation work was painstaking and time-consuming, it had a profound impact on the quality and security of any predictions that might then be made from the genetic code.

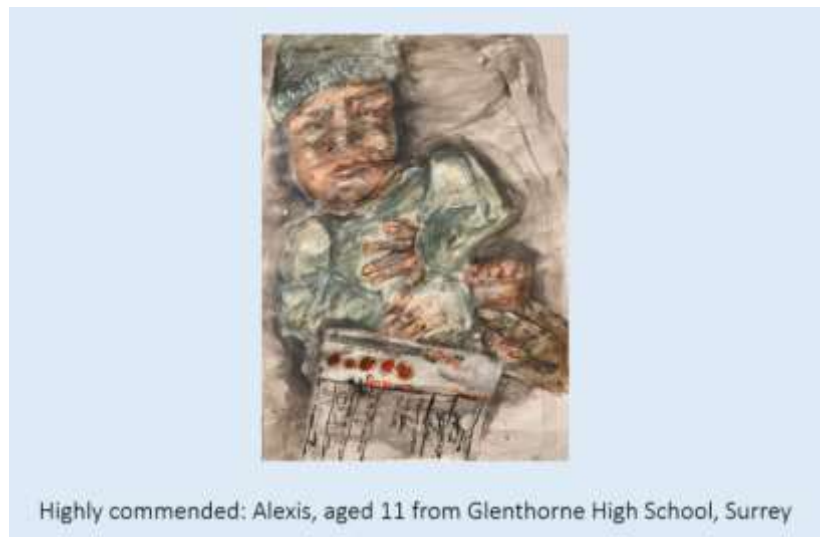


Challenge of managing uncertainty when incorporating expanded genetic screening into CF Newborn Bloodspot Screening

Dr Jane Chudleigh, King's College London

Jane spoke about her work exploring the experiences of families receiving diagnoses of cystic fibrosis and CFSPID (CF screen positive, inconclusive diagnosis) via current newborn screening pathways. She discussed how the number of children with CFSPID is a function of decisions as to how much uncertainty to tolerate as a price for identifying children with true cystic fibrosis. Drawing on her research with patients and families, she highlighted the need to make it clear at the outset of screening that answers may not be definitive, and the

importance of support for parents as they navigate challenging outcomes from newborn screening. She described the nomadism some CFSPID families experienced, feeling they did not fit fully in the 'CF world' or the 'healthy child' world, but flitted between the two. Jane reflected that while a finding of CFSPID could be anxiety-provoking, some parents described how it helped them advocate for their child at times when they were unwell, and in general the families she interviewed (encompassing people with CF and with CFSPID) preferred an approach to newborn screening that would detect more babies with true CF, despite this meaning more children living with CFSPID.



The challenges of living with a rare disease diagnosis

Dr Sarah Wynn, Chief Executive Officer, Unique

Sarah then talked to us about her work with families affected by rare conditions, describing the convoluted route that many had experienced in reaching a diagnosis, and reflecting on the importance of reducing these diagnostic odysseys. She described how valuable a diagnosis could be for families, both in terms of informing treatment and care plans, but also in other ways such as having an explanation, allowing them to connect with others going through similar experiences, and supporting reproductive decision-making. She described the complexity of experiencing a genetic diagnosis, which while opening up new options may also bring new uncertainties, partly in view of the paucity of information available about how very rare conditions might affect a child over the years. She reflected how people had a wide range of views and experiences in this area, noting that while prompt diagnosis of symptomatic children was really important, looking back, some families really valued the time they had had with their child before symptoms started and the possibility of a genetic condition had been raised.

The challenge of providing clinical care in situations of uncertainty

Dr Robin Lachmann, Consultant in Inherited Metabolic Disease, National Hospital for Neurology and Neurosurgery, Queen Square, London

Robin concluded the talks for this session, discussing his experiences of providing clinical care to adults with metabolic disorders. A key example Robin discussed was Pompe disease, a condition which will be screened for by the Generation Study, through which he illustrated the huge variability inherent in many metabolic conditions. He described how some people with Pompe disease will die of heart disease in the first years of life, while others may have a healthy childhood but go on to develop muscle problems in later life. He outlined how early enzyme replacement therapy can be life-saving for babies with Pompe disease but is less effective at treating muscle problems in adults, and illustrated the quandary that in seeking to identify and treat babies with heart problems, screening would also identify babies who were currently healthy but who would go on to develop muscle problems perhaps many decades in the future, and for whom there may not be effective treatment.



Following the talks, we had a panel discussion where the speakers were joined by **Dr Judith Hayward, RCGP joint clinical representative in Genomic Medicine**, and **Dr Jonathan Roberts, Research Genetic Counsellor, The Synapse Centre for Neurodevelopment**, to reflect on the question: '*How should we prepare parents and the NHS for navigating new uncertainties?*' Key points arising included:

Screening should not be necessary to avoid diagnostic odysseys

- Getting timely and efficient genomic sequencing for children *who have symptoms* suggestive of a rare condition should be a top priority.
- With appropriate access to genomic testing, the diagnostic odyssey should not be long for children presenting with comparatively well described rare conditions such as those screened for in the Generation Study and similar projects.
- Where diagnostic odysseys remain, this should be because our understanding around how genomic variation impacts on health is still evolving and it is not possible to make a genomic diagnosis at this time – it should not apply to any diagnoses that stand to be made via newborn genome sequencing projects.

- We must ensure that initiatives such as newborn genome screening do not compromise diagnostic genomic testing for people living with overt rare conditions.



Focus 3: the opportunities and questions raised by screening using genomes as opposed to more targeted options

Our final session, chaired by **Professor Caroline Wright**, explored the potential benefits of research with genomic data, and the complexities of asking consent for genomic data collection from healthy babies.

Caroline introduced the session with a brief reminder that a genome sequence is not in itself a test, it is an *assay* in which we determine the individual bases of a person's genetic code. A test is where we ask clinical questions of that sequence: the variants we examine in doing so could range from a single variant, to many thousands of variants. Caroline reminded us that it is possible to develop assays specific to a test question, at one extreme only examining specific variants of interest. Such an approach is inherently limited as one cannot ask questions of data that have not been collected. In contrast, when using genomes as an assay, this generates huge amounts of data with almost no limit to the questions you can ask of them, and as such is incredibly useful for agnostic discovery science. Yet challenges arise in working out which questions are appropriate to ask of such data, especially since every 'healthy' adult has multiple hypothetically concerning genomic variations that for reasons that are poorly understood do not lead to detriment in practice. Where should the balance between specificity and discovery lie in developing an assay for newborn screening?



Highly commended: Parampreet, aged 11 from Higham Lane School, Warwickshire

Publics views about contributing genomic data for research

Dr Richard Milne, Head of Research and Dialogue, Engagement and Society, Wellcome Sanger Institute

Richard talked about his research exploring people's willingness to contribute towards genomic datasets and what they expect to be done with their data, focusing particularly on questions of trust. He shared results from the 'Your DNA Your Say' study indicating that around 50% of UK adults would be willing to donate genomic data for use by doctors; slightly fewer for academic research; and considerably fewer for 'for profit' research. People who were more familiar with genomics, and people who were more trusting, tended to be more willing to donate their data. Return of results did not have a straightforward link with willingness to contribute, suggesting such decisions were not simply transactional, but trust was needed in order to have delayed reciprocity. Information about who would benefit from data access; knowing who is using data and for what purpose; and the option to withdraw data were all ranked as important factors in helping people trust.

Ethical considerations for projects involving 'healthy' babies

Professor Dominic Wilkinson, Director of Medical Ethics, Oxford Uehiro Centre for Practical Ethics

Dominic spoke about the challenges of involving 'healthy' babies in screening and research. He discussed how newborns cannot give consent for themselves: adults will need to make decisions on their behalf, and this will involve parents weighing up the benefits and harms on behalf of their child. For screening, he outlined that this meant weighing the rare but high magnitude benefit of early life treatment before onset of symptoms improving outcomes, against more frequent smaller harms such as relationships potentially being affected at a critical stage for bonding, and medicalisation of children with uncertain findings. Regarding research initiatives, he described how traditionally benefits are

assumed to be elsewhere, rather than for the participating individual, and only a minimal level of risk would usually be considered acceptable for patients who cannot consent for themselves. He discussed challenges relating to consent conversations involving decisions for 'healthy' newborns, for example deciding on the optimal time to have conversations, and how much information to provide, making the point that one size will not fit all. He also reflected that while lengthy in-depth consent conversations may be possible in a research context these would be difficult to deliver in the context of a population screening programme.

The research-clinical relationship in genomics: hybrids and alloys

Professor Michael Parker, Director of the Ethox Centre, University of Oxford

Michael discussed the blurring boundaries between research and clinical care, inviting us to consider options for rethinking their relationship. He outlined reasons why they have historically been treated as distinct, with different primary objectives, requiring different balances, and hence developing different consent standards, oversight mechanisms and accountability structures. He discussed how genomics drives convergence of research and clinical care, and offered two models for the audience to consider: a hybrid model, where research and clinical practice remain distinct but increasingly connected; and an alloy model, where research and clinical practice fully merge into a new unified enterprise. He discussed how a hybrid model might provide ethical clarity but involves considerable duplication of processes and procedures, and potential missed opportunities for innovation. He described how an alloy model would allow more efficient, coordinated and comprehensive use of data, with the potential for new forms of patient/participant involvement and agency, but perhaps at the expense of diluting important protections. Michael invited us to consider which values should guide our choices between these different models, who should be involved in such decisions, and how governance might helpfully develop as research-clinical relationships in genomics evolve.



Highly commended: Nadia, aged 11, from Cheney School, Oxfordshire

The session concluded with a panel discussion in which the speakers were joined by **Dr Meekai To, Principal Clinician in Maternal and Child Health, Genomics England**, and **Dr Celine Lewis, Principal Research Fellow in Genomics, UCL Great Ormond Street Institute of Child Health**. The starting question for the panel was: *'How can newborn genome studies support parents to engage with what it means to contribute genomic data, as well as what it means to have expanded screening?' Key points under discussion included:*

Should an offer of screening rest on agreement to take part in research?

- There were a range of perspectives regarding the acceptability of bundling a screening offer with the contribution of genomic data. We discussed that where screening is being offered in a research context, as part of a research study, and genomic data is necessary to fulfil research aims (such as the Generation Study), this may be an argument for tying these together. However, it was recognised that newborn screening research has clinical overlap in aspiring to directly influence the clinical care of participating babies, and the more 'clinical' a test becomes the more carefully we need to consider the fairness of twinning it with whole genome data collection and its contribution to research endeavours.
- A spectrum of models for the research-clinical relationship were considered, from distinct separation on one hand to the 'alloy' model (full merging to create a new enterprise) on the other. The panelists considered whether at least some aspects of the health service should

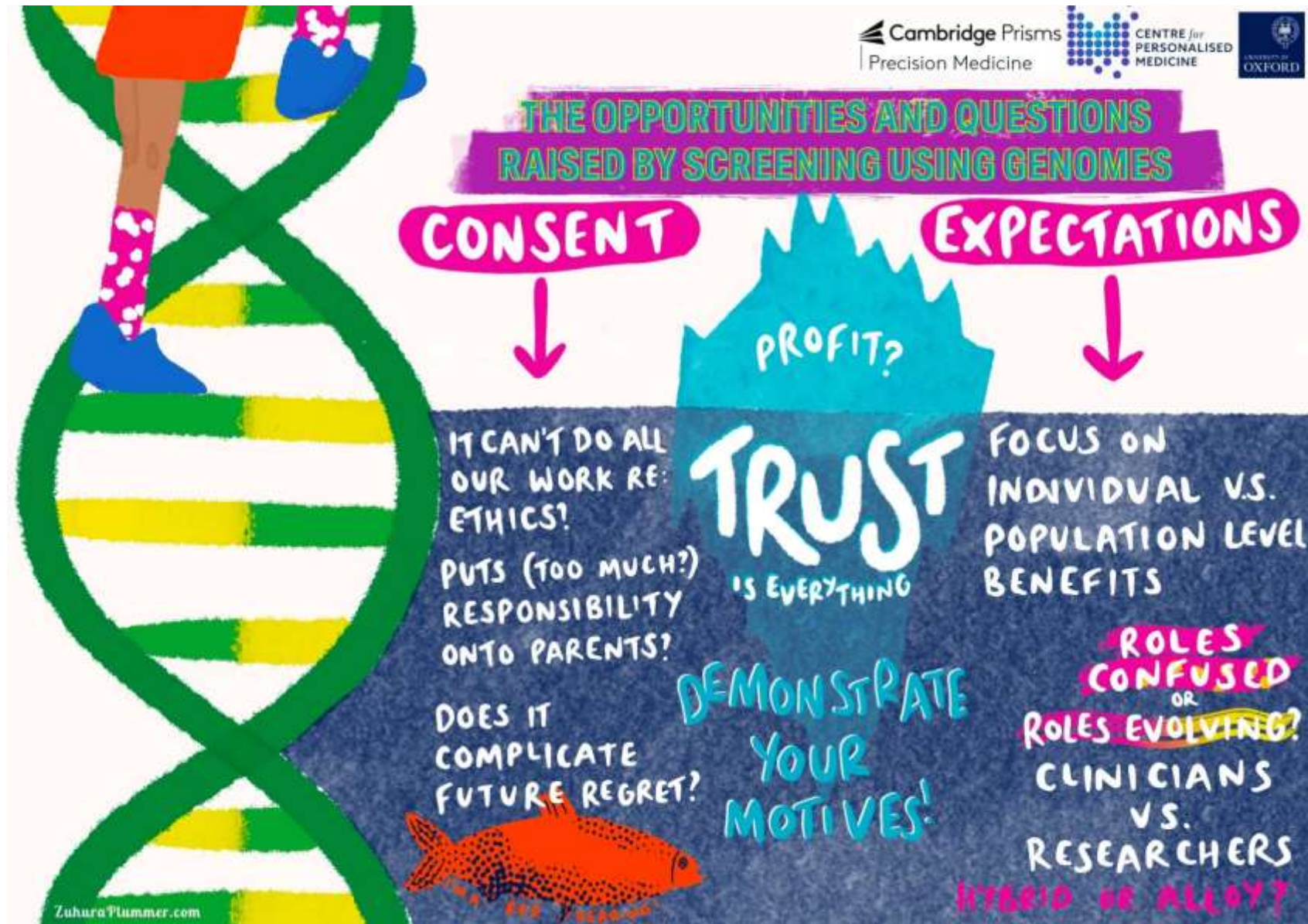
follow an alloy model, with a need for public conversations around how much data sharing is appropriate. Attempts to maintain absolute privacy may be in tension with realisation of health benefits for us all, and we need to explicitly consider how much health we are willing to give up in order to protect our privacy.

What is a 'result' in the context of a genome sequence?

- We each have millions of variations in our genome, raising questions of how and when we should construe variations as being a 'result' in cases where a genome is our assay. Given evidence from population studies that everyone has a sizeable number of hypothetically concerning genomic variations which do not seem to lead to ill effects, presumably because of other modifying factors, what features and contexts make it appropriate to conceptualise particular variations as a result of a screening test in a 'healthy' person?
- While there may be good reasons to communicate results from genomic initiatives, a transactional perspective that projects need to give something back in order for people to participate is not necessarily correct. There should be a commitment to reciprocity, but this may not have to be immediate.
- The panel considered how participating babies would become more involved in decisions around their ongoing participation as they transition to adulthood. How might a genome sequence have value across the life course of an individual, and how might age and evolving health status influence when and why genomic variation(s) might be construed as results?



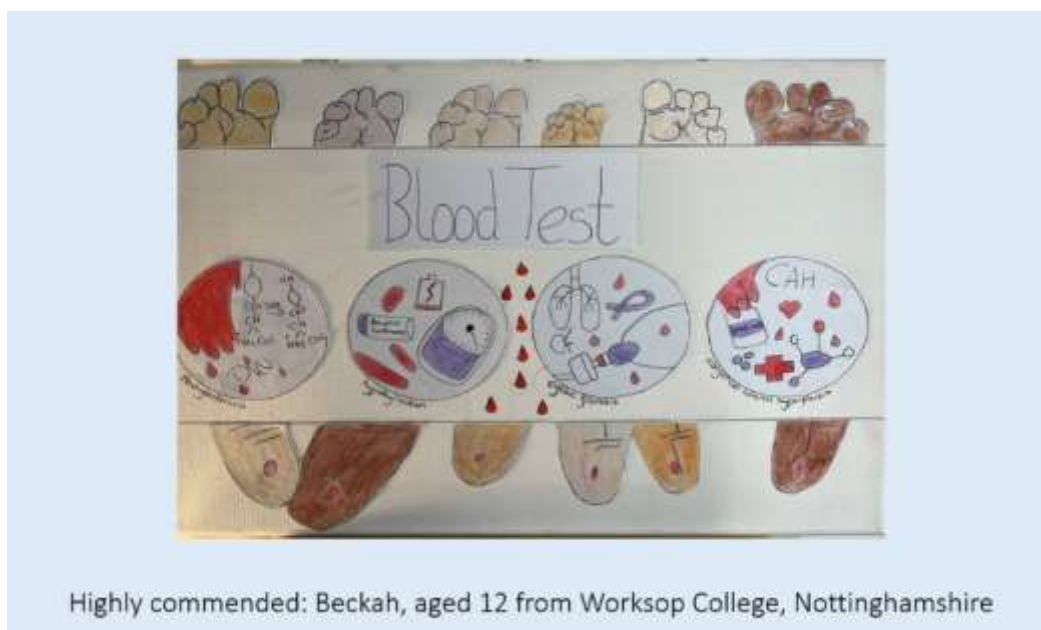
Highly commended: Ariyan, aged 13 from Oaklands Secondary School, London



Concluding notes

We enjoyed very constructive discussions throughout the day. A number of principles seemed to resonate widely:

- **It is of paramount importance that children with symptoms suggestive of a genetic condition have timely access to genomic testing.** Screening should not be necessary to avoid long diagnostic odysseys: the sorts of diagnoses that would be identified by a newborn screening programme should be rapidly identified by diagnostic genomic testing of a symptomatic child.
- **We should anticipate that in some cases, using genomics for newborn screening will lead to uncertainty for families and the health service.** It is important to prepare parents for this through careful consent conversations, and to do our part to shift prevailing deterministic discourses around genomics that may set people up to expect certainty.
- **Generating evidence around how genomic variation links to disease in a 'healthy' population will be hugely valuable.** Research where data are collected such that we can ultimately learn how a baby's genetic code relates to their future health stands to benefit future generations. Given the scale of data needed to make progress on such questions, international collaboration will be important.
- **Screening has opportunity costs and we must ensure that when aspiring to improve child health through newborn screening we do not inadvertently compromise it by diverting resources from other potentially more impactful areas.** In particular, it is essential that efforts to extend newborn screening do not distract from making prompt genetic diagnoses for symptomatic children.



Highly commended: Beckah, aged 12 from Worksop College, Nottinghamshire

There were various areas where benefits and harms were recognised as being in tension, with participants having a range of ideas as to where the balance should lie:

- **How should we balance rare but highly significant benefits, such as diagnosing conditions where early treatment improves outcomes, against more common but smaller harms, such as generating ultimately spurious concerns around a baby's future health?** The aspiration of newborn genome screening to do better for families affected by rare conditions was

recognised, but participants held differing views regarding the likelihood that benefits would be realised, and the extent of the harms that might arise.

- **How should we balance the need to collect better evidence to inform screening decisions in the future, against using weaker evidence to try to benefit babies in the here and now?** Discussions recognised a tension between waiting to generate 'perfect answers' regarding variant penetrance in a newborn population such that some babies miss out on early diagnosis and treatment, and 'jumping the gun' meaning that we lose opportunities to work out which screening tests are truly beneficial.
- **How should we balance privacy concerns against potential health benefits?** The huge scientific value of genomic databases linked to health outcomes was evident throughout the day, and any genomic screening on offer is only possible because others have allowed research using their genomic data. Yet the screening offered by the Generation Study (and other newborn genome screening studies) would not require a whole genome as the assay – is it fair for the offer of screening to be contingent on contribution of a baby's genome to a research database?



To summarise, while the topic of newborn genome screening generates lively debate, participants attending this event shared considerable common ground. They were united in their wish to improve outcomes for people and families living with rare conditions, and to ensure that efforts to do this do not negatively impact on 'healthy' babies and their families. While there were significant differences of perspective regarding how best to achieve this, discussions on the day demonstrated that on many important points we already share a degree of consensus.

We hope to revisit newborn screening in future Centre for Personalised Medicine events – please sign up to our mailing list, follow us on social media, or keep an eye on our website to find out more.



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