Beyond One Million Genomes

D1.5

Stakeholders trust in genomic data sharing landscape analysis

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Abstract

This scoping report represents a mission-oriented approach to supporting citizens' engagement and public trust in genomic data sharing, scoping out and suggesting possible approaches. It recognises from the outset that the issues of engagement and trust extend beyond the indispensable involvement of citizens to embrace a much wider range of stakeholders whose buy-in will also be essential to success. This review takes account of the B1MG and 1+MG, and aims to offer conceptual and practical steps for building on those achievements to bridge potential and actual benefits to science and society with a specific focus on citizens.

1. Executive Summary

The rapid progress that has been made in genomics over the past two decades has created much debate (Boccia, 2014[1]). On the one hand, genomics has the potential to deliver earlier diagnosis, more effective prevention programmes and more precise targeting of therapies, in some cases challenging our understanding of the nature of certain diseases. On the other hand, it raises a range of ethical, social and legal challenges (ELSI), including among other issues, protection and ownership of data, the need for care in interpreting data, potential misuse of data by commercial organisations, especially insurance companies, and questions about autonomy and the potential for stigma (National Research Council, 1988). As insights from genomics are increasingly used in clinical settings to inform personalised medicine, these ELSI considerations have been broadened, with many concerned this will widen existing inequalities in health care (Brothers & Rothstein, 2015[2]).

While genetic testing may improve disease prediction, diagnosis, and treatment, the rapid uptake and application of genetics and genomics raise numerous ethical, legal, and social issues (ELSI). One of the most prominent among these is the growing number of possibilities of using genetic information to justify treating individuals differently or profiling specific population groups that may lead to genetic discrimination (GD) (Kim, 2021[3]).

The EU's General Data Protection Regulation (GDPR) is an important regulatory change at the EU level that has significant implications for the processing of genomic data in research and clinical practice. Recital 51 of the GDPR designates personal data which is, by its nature, particularly sensitive in relation to fundamental rights and freedoms as requiring specific protection, as the context of its processing could create significant risks to those fundamental rights and freedoms. Beside data generation and processing, ensuring data privacy and security requires robust infrastructure, training, as well as careful regulation of access.

To capture the full benefits of genomic data, it must be shared with multiple actors, including: researchers to support academic and clinical research; health providers to support delivery of health services and public health activities; and commercial organisations involved in developing and implementing new health technologies or delivering health care services (Williams et al, 2021[4]). Data sharing to facilitate greater genomic research and translation of findings into clinical use

[1] https://academic.oup.com/eurpub/article/24/3/349/478117?login=true
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4296905/
[3] https://www.nature.com/articles/s41525-021-00218-4#Bib1
[4] https://apps.who.int/iris/bitstream/handle/10665/338975/Policy-brief-38-1997-8073-eng.pdf?sequence=1&isAllowed=y

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relies on the implementation of advanced technological solutions, health workers with the right skills and training to contribute to implementation, the active involvement of citizens and patients that support translation, and implementation of strong regulatory and governance procedures (Raza & Hall, 2017[5]).

In this context, it is unavoidable to mention the concurrent COVID-19 pandemic, in view of the evolution of public awareness of science, as hopes have grown for vaccines and treatments to counter COVID-19. But this enhanced awareness carries corresponding responsibilities alongside the obvious potential benefits for mustering support for science.

The pace of change, already increasingly rapid as science opens ever more doors to understanding of health, disease, diagnosis and treatment, has received dramatic new impetus through the exigencies of the COVID 19. Never in modern times has the population of the planet been subject to such a direct threat to health, and never have science and technology responded with such alacrity, energy and effectiveness. As the European Council secretariat explains in updating on progress towards an international agreement on pandemics, "the sharing of pathogens, biological samples and genomic data as well as the development of timely medical solutions (vaccines, treatments and diagnostics) are vital in order to enhance global pandemic preparedness." (https://www.consilium.europa.eu/en/policies/coronavirus/pandemic-treaty/)

The corresponding leap in citizens' awareness and expectations of the world of science is however presenting a new dilemma: while health policy is encouraging and promoting (and indeed very largely depending on) science to solve the unprecedented challenge that COVID 19 presents, it also has to cater to the importance of bringing society along with developments, to foster understanding and to counter scepticism, suspicion, doubt and even hostility. This concern informs the European Parliament resolution on strengthening the fight against cancer, adopted by the plenary on 16 February 2022. It "encourages the Commission and the Member States to promote the knowledge of cancer biology through the implementation of genomics and informatics infrastructures; urges all implementation partners to be ever mindful of the principles of data privacy and security, trust, transparency, patient centricity and patient involvement at all times."
(https://www.europarl.europa.eu/doceo/document/TA-9-2022-0038_EN.html)

Against this background, it is prudent to consider the risk that the application of genome technology to healthcare, despite all its multiple potential benefits as a breakthrough in healthcare, could be confronted with similar turbulence and even negative opinion unless meticulous attention is paid to the challenges of gaining public understanding.

Public understanding is vital in itself to gain trust on this data acquisition – but it is also an indispensable condition for obtaining the policy support that genomic medicine demands for implementing this ambitious project.

At the heart of the 1+MG/B1MG concept is the collection and exchange of citizens' data. It is consequently implicit in the logic of the exercise that the interests of the citizens – whose data is to be collected and exchanged – should receive priority attention, even while solutions are found to the myriad technical, scientific, legal and political issues that the project also raises.

This paper brings focus to this dilemma in European terms, scoping out both the potential and the challenges, and suggesting some approaches that can improve the chances of successful

[5] https://academic.oup.com/bmb/article/123/1/35/4080201

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conciliation and mutual understanding between science and citizens – with the attendant benefits accruing to society as a whole.

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2. Contribution towards project objectives

With this deliverable, the project has reached or the deliverable has contributed to the following objectives/key results:

	Key Result No and description	Contributed
Objective 1 Engage local, regional, national and European stakeholders to define the requirements for cross-border access to genomics and personalised medicine data	**1.** B1MG assembles key local, national, European and global actors in the field of Personalised Medicine within a B1MG Stakeholder Coordination Group (WP1) by M6.	Yes
	2. B1MG drives broad engagement around European access to personalised medicine data via the B1MG Stakeholder Coordination Portal (WP1) following the B1MG Communication Strategy (WP6) by M12.	Yes
	3. B1MG establishes awareness and dialogue with a broad set of societal actors via a continuously monitored and refined communications strategy (WP1, WP6) by M12, M18, M24 & M30.	Yes
	4. The open B1MG Summit (M18) engages and ensures that the views of all relevant stakeholders are captured in B1MG requirements and guidelines (WP1, WP6).	Yes
Objective 2 Translate requirements for data quality, standards, technical infrastructure, and ELSI into technical specifications and implementation guidelines that captures European best practice	**Legal & Ethical Key Results**	
	1. Establish relevant best practice in ethics of cross-border access to genome and phenotypic data (WP2) by M36	Yes
	2. Analysis of legal framework and development of common minimum standard (WP2) by M36.	No
	3. Cross-border Data Access and Use Governance Toolkit Framework (WP2) by M36.	No
	Technical Key Results	
	4. Quality metrics for sequencing (WP3) by M12.	No
	5. Best practices for Next Generation Sequencing (WP3) by M24.	No
	6. Phenotypic and clinical metadata framework (WP3) by M12, M24 & M36.	No
	7. Best practices in sharing and linking phenotypic and genetic data (WP3) by M12 & M24.	No
	8. Data analysis challenge (WP3) by M36.	No
	Infrastructure Key Results	
	9. Secure cross-border data access roadmap (WP4) by M12 & M36.	No
	10. Secure cross-border data access demonstrator (WP4) by M24.	No

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Objective 3 Drive adoption and support long-term operation by organisations at local, regional, national and European level by providing guidance on phased development (via the B1MG maturity level model), and a methodology for economic evaluation	**1.** The B1MG maturity level model (WP5) by M24.	No
	2. Roadmap and guidance tools for countries for effective implementation of Personalised Medicine (WP5) by M36.	No
	3. Economic evaluation models for Personalised Medicine and case studies (WP5) by M30.	No
	4. Guidance principles for national mirror groups and cross-border Personalised Medicine governance (WP6) by M30.	No
	5. Long-term sustainability design and funding routes for cross-border Personalised Medicine delivery (WP6) by M34.	No

3. What Europe has done

Many of Europe's achievements and commitments have been exemplary in the development of health-related science, technology and regulation, and the European Union is on the brink of providing further stimulus both to technology development and to the role of the EU in health policy. B1MG has already played its part in this evolution, driving a new and cooperative approach to many aspects of bridging technology and the citizens that the technology is intended to serve – as outlined in section 2, above. This concept of cooperation is at the heart of B1MG Stakeholder Coordination Group as it actively seeks engagement of the widest range of stakeholders, and offers a link to a community that gives everyone a chance to share ideas and influence the direction of the project. There are now great expectations of the promise EU Health Data Space[6], the European Health Union[7], the Pharmaceutical Strategy[8], and the Cancer Mission[9] and EU Beating Cancer Plan[10].

The European Health Data Space, on which a legislative proposal is scheduled for April 2022, will promote better exchange and access to different types of health data (electronic health records, genomics data, data from patient registries etc.), not only to support healthcare delivery in terms of primary use of data but also for health research and health policy making purposes through secondary use. The entire data system will be built on transparent foundations that fully protect citizens' data and reinforce the portability of their health data, as stated in article 20 of the General Data Protection Regulation (GDPR). The Commission, in collaboration with the Member States, is engaged in the preparatory work and development of the European Health Data Space, supported by a Joint Action for the European Health Data Space to facilitate the sharing of health data for public health, treatment, research and innovation in Europe. The basic pillars of

[6] https://ec.europa.eu/health/ehealth-digital-health-and-care/european-health-data-space_en
[7] https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en
[8] https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe_en
[9] https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/eu-missions-horizon-europe/cancer_en
[10] https://ec.europa.eu/commission/presscorner/detail/en/ip_21_342

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the European Health Data Space will be a strong system of data governance and rules for data exchange, data quality, and strong infrastructure and interoperability.

Specifically in the area of genomics, the EU is now backing efforts to synthesise the exploitation of genetic and clinical data across Europe in ways that open unprecedented opportunities for improved healthcare of its citizens. Following the success of the 1+ Million Genomes Initiative (1+MG)[11], under which 24 European countries have committed to grant cross-border access to one million sequenced genomes by 2022, the Beyond 1 Million Genomes (B1MG)[12] project is helping, with funding from the Horizon 2020 programme, to create a network of genetic and clinical data across Europe that will make it easier to share human health data and reap the benefits for care and for research.

This will enable scientists to better understand diseases - particularly rare diseases, where only nationally-available data may not provide sufficient data. This enhanced understanding will allow clinicians to take account of the patient's particular genetic and phenotypic data, permitting greater accuracy of diagnosis and specifically targeted treatment or preventive medicine. This personalised medicine is predicted to lead to a longer life expectancy and a better quality of life for European citizens. At the same time, the data sharing will stimulate innovation in the healthcare industries, and boost the European economy with better targeted care easing the strain on national health services. Through this cooperation it will become possible to develop long-term guidance on phased development and a methodology for economic evaluation.

This is part of the EU's agenda for the Digital Transformation of Health and Care[13], and 1+MG/B1MG is intended to create long-term means of sharing data beyond 2022, enabling access to a still wider range of genomes. It is aiming to create the necessary infrastructure, legal guidance and best practices so that scientists and clinicians can study the genotypic and phenotypic data of large populations, allowing genetic data from one individual to be matched with their phenotypic data (such as weight, blood group and medical history).

To be transformative in the healthcare sector, genomic and linked phenotypic data need to be accessible for analysis and interpretation at a scale that has not yet been attained. The essence of this European project is to work with regional, national and European stakeholders to augment the flow of data. It will provide sufficient scale for new clinically impactful research. The project envisages developing and connecting national data-sharing networks so that data remains stored locally but is accessible across Europe, addressing concerns related to the movement of data.

Cooperation is at the heart of B1MG Stakeholder Coordination Group. Its partners are public, academic and industrial, and it actively seeks engagement of the widest range of stakeholders, offering a specific 'Stakeholder Portal'[14] to generate a community that includes patient organisations, clinicians, academics, industry and funders, as well as the project participants, giving everyone a chance to share ideas and influence the direction of the project.

[11] https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes
[12] https://b1mg-project.eu/
[13] https://wayback.archive-it.org/12090/20201130160159/https://ec.europa.eu/digital-single-market/en/european-ehealth-policy
[14] https://sites.google.com/ebi.ac.uk/b1mg-stakeholders-portal/home

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Explicit aims of the project include ensuring that the general public and policy makers in member states and signatory countries are well informed about genomics, and to allow its uptake by healthcare systems and integration into personalised healthcare. Its central thesis is that the EU's genomic collaboration and research have to be citizen-focused and patient-friendly.

Health literacy of European citizens has been the focus of several EC recommendations that aim to increase their empowerment and enhance the digitalisation of healthcare sectors, through the provision of secure access and data sharing procedures, and the development of digital tools for their engagement and participation in healthcare process (The Horizon 2020 Work Programme (2014–2015)[15] , The Horizon 2020 Work Programme (2016–2017)[16]). Improving citizens' literacy will enable them to make appropriate and well-informed health decisions and play an active role in health management. Policies, programs, standards and initiatives related to Personalised Medicine in Europe, with a particular attention towards citizens' literacy and engagement are the main focus of an EU funded project "IC2PerMEd"[17]. Among EU member states, Italy has been the first country to address health literacy in Personalised Medicine within the national policies published in 2013 (Mazzucco et al, 2013[18]), followed by other countries that addressed the importance of citizens' engagement in informing and shaping national health systems approaches to Personalised Medicine.

4. Turning intentions into action – Engaging stakeholders

The noble ambitions of bringing wide publics on board in policy formulation and implementation need careful nurturing if they are to be optimally realised.

A pan-European genomic initiative raises ethical, legal and social issues as sensitive human data will need to be accessed across national boundaries and diverse legal challenges, and citizens' needs should be kept at the forefront in the necessary arrangements. It will need agreement on technical specifications and implementation guidelines that capture and advance European best practice in terms of data quality, standards, and technical infrastructure, and respond to the ethical, legal, and social implications, including for protection of personal data, security of stored data, ethical use of data and clear data ownership rules.

This cannot be successfully embarked upon without citizen engagement and will never be successfully implemented without citizens' trust.

[15] https://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/main/h2020-wp1415-intro_en.pdf
[16] https://ec.europa.eu/research/participants/data/ref/h2020/wp/2016_2017/main/h2020-wp1617-intro_en.pdf
[17] https://www.ic2permed.eu/
[18] https://pubmed.ncbi.nlm.nih.gov/23466031/

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4.1 Citizen engagement in context

Engagement is defined as the "process by which people are enabled to become actively and genuinely involved in defining the issues of concern to them, in making decisions about factors that affect their lives, in formulating and implementing policies, in planning, developing, and delivering services, and in taking action to active change" (WHO, 1992). Multiple actors seeking public participation can contribute to citizen engagement. The aims of this process can range in impact on the decision-making from consultation ("I acknowledge your concerns and aspirations and I will consider them in my decision) to empowerment ("I will implement what you decide") (IAP2, 2018). This is substantially different from educating and informing the public in a top-down fashion. Citizen education/information could be seen, at most, as a very initial form of engagement requiring from the citizen the availability to listen and learn.

Personalised medicine requires engaged, informed and empowered patients that contribute not only to their own health, but also to knowledge creation and potentially its governance. This can be only based on adequate understanding, for which health literacy is vital.

4.2 Health Literacy

Citizens' behaviours and practices in relation to Personalised Medicine belong to three overarching themes, namely 1) citizens' engagement in their own health, 2) contribution to the research endeavour, and 3) engagement in design and development of PM (Budin-Ljøsne and Harris 2015). Thus, citizens are required to participate in decision-making processes, research projects, and debates, for an appropriate use of new technologies and the management of their health information, contributing in collaborations with researchers, health professionals, public health authorities, and drug manufacturers through involvement in patient advocacy groups, advisory boards, and HTA bodies (Boccia S. 2020).

Education, support and training are key drivers of acceptance of novel processes, and the B1MG Stakeholder Coordination Group will have a central role in initiating such activities.

Education and communication should go hand in hand, to raise awareness, generate a common understanding and build capacity across professional communities, policymakers and the general public.

The experts and communications channels of allied organisations should be recruited to leverage support from the existing communication and outreach programmes of stakeholder members to support the ambition of the 1+MG as well as the EU Health Data Space.

Standard suites of communication tools will be needed, ranging from logos and slide presentations to social media presence and rolling updates, augmented by on-line discussion forums aligned with agreed guidelines.

Specific sub-audiences should be catered for with customised information respecting their distinct backgrounds.

Policy makers merit special attention, with communication strategies to raise awareness of the benefits to be obtained from genetic data-sharing. Policy briefs specifically targeting policy makers in each country should focus on specific issues.

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4.3 Importance of Citizens engagement

The importance of citizen engagement in large-scale plans has long been recognised in the EU, but the delivery has not always reached expectations or matched the ambitions.

The risks of lack of engagement are amply demonstrated by specific cases ranging from the persistent consumer resistance that continues to paralyse EU decision-making on genetically modified products, where member state governments fear they lack a popular mandate for giving approval, to the collapse of efforts to reach the Anti-Counterfeiting Trade Agreement in 2012. Most obviously, today, the anti-vax movement is still negatively influencing take-up of COVID 19 vaccines, notably among populations most likely to benefit from it and who prove vulnerable to misinformation driven by conspiracy theories or more malign and deliberate influence from beyond the EU.

One of the most delicate discussions where citizen engagement has become crucial is in the use of personal data. Rare disease patients are for obvious reasons often more willing to share their data than the general population (The Eurordis Rare Barometer poll[19] showed 97%in comparison to 80% in the general population. However, the survey, providing 2000 answers covering 66 countries, also underlined the importance to people of their own sense of data ownership and the possibility to control the purposes for which it is used, as well as different degrees of trust for profit versus non-profit users.

Patients and citizens have been consistently vocal in their concerns about their own data being taken out of their control and being exploited without their consent, for purposes they have not subscribed to, or at a country - and a fortiori at an EU – level (as highlighted in Special Eurobarometer 431 on Data Protection[20]). The concerns have led to the creation of systems of control – most notably in EU initiatives such as the GDPR[21], which provided a framework for data protection principles in an attempted balance with the free cross-border flow of personal data within the EU.

Where the data relates to an individual's health, the concerns over privacy are all the more acute, and need to be balanced against the broader benefits to society that can come from the sharing of health data. The fact that many innovations, technologies and new drugs that are developed using genomic data are developed by private companies and not by universities or hospitals makes the involvement of private companies in genomic research essential, and very often requires these companies to access publicly owned genomics databases. Yet, people may be less willing for their genomic information to be used in research if private companies are involved, due to concerns over privacy and the uses to which their data may be put, especially if it is used to generate financial profit for these companies that may not benefit society. Research into public attitudes to commercial access to health data in the UK illustrates this dilemma (Ipsos MORI, 2016[22]). This research found four 'key tests' that citizens applied: first, whether the use of data was for a clear public benefit. Second, whether the actors involved were trusted to be acting in the public interest. Third, how anonymized or aggregated the data concerned was. And fourth, effective safeguarding of the data. Genomic information was seen as particularly sensitive,

[19] http://download2.eurordis.org.s3-eu-west-1.amazonaws.com/rbv/20-01-24 RB Data Survey Fact Sheet_Final.pdf

[20] https://data.europa.eu/data/datasets/s2075_83_1_431_eng?locale=en

[21] https://eur-lex.europa.eu/eli/reg/2016/679/oj

[22] https://www.ispor.org/publications/journals/value-in-health/abstract/Volume-23--Issue-9/Improving-Transparency-to-Build-Trust-in-Real-World-Secondary-Data-Studies-for-Hypothesis-Testing-Why-What-and-How-Recommendations-and-a-Road-Map-from-the-Real-World-Evidence-Transparency-Initiative

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precisely because the potential uses of the data in the future were so unpredictable. Further citizens' views are reported in a literature survey and an Ipsos Mori survey on public dialogue in genomics commissioned by Genomics England.

It is vital therefore, for the genomic medicine field to develop, to ensure that trust is established through communication and information, for instance to help alleviate these concerns and build trust in data sharing with private companies, it is important that patients and the public are educated on the huge benefits that may result from genomic research, and the potential contribution of private involvement in genomic initiatives to the public good and to benefiting health and health care. For people contributing to such studies, it should be made clear when they consent that very often they may not benefit themselves directly. This may not be a problem as many people have indicated in surveys that they support research in general.

At the same time, private companies should talk to and collaborate with other stakeholders, including patients and the wider public, to ensure the values and concerns that people have surrounding the use of their personal data are reflected in genomic initiatives.

In addition, it should be ensured that private-sector actors adhere to codes of good conduct, have transparent governance and monitoring procedures, and demonstrate the value of their research in terms of benefiting health and health care, in order to increase trust in private actors acting in the public interest. In this context, the example of the FinnGen project in Finland highlights both the benefits of and good practice in involving private companies in genomic research (FinnGen, 2020[23]).

4.4 Information and Education

Information and education will be needed: in their absence, no real understanding can be generated among the stakeholders. While it is nowadays axiomatic that education of citizens is essential to allow appropriate decisions about their own health, the realisation of that goal is still in many respects distant. The underlying issue of public trust is subject to many different interpretations, and in the absence of wider consensus and more precise understanding, trust may indeed be said to remain "in the eye of the beholder."

A study developed within the Italian National Center for Disease Prevention and Control (CCM) project, titled “Capacity building and citizens-omics: innovative actions for the literacy of health professionals and citizens in the era of omics sciences” evaluated citizens’ knowledge, attitudes, and educational needs in the field of omics sciences, and attitudes and perceptions about genetic and/or omics tests (Calabrò et al, 2020[24]). This systematic review revealed limited knowledge, clear gaps, and controversial opinions about their use, and underlined the need for strengthening public engagement. CCM project also aims to identify and summarise the past and ongoing initiatives in the field of omics sciences, addressing citizens’ literacy.

Citizens’ literacy and engagement is also one of the focus of a European project, “European network staff eXchange for integrAting precision health in the health Care sysTems”[25] (ExACT), that aim to identify the key elements of innovative models of citizen engagement in precision health. Preliminary results of a systematic review show a substantial variability in the way through which citizen engagement occurs, with most of the initiatives being conducted in the UK. The review identified eight engagement initiatives, ongoing or recently concluded, that varied in

[23] https://www.finngen.fi/en
[24] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7644959/
[25] http://www.exactproject.net/site/

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the way through which citizen engagement occurred and was reported. The engagement methods used in the identified initiatives were open discussions, citizen forums, more commonly through digital tools such as tablet apps and online platforms, surveys with audio-visual tools and advisory board involvement. The majority of these initiatives were aimed at gathering citizen perspectives to inform policy making, or at establishing current public understanding on precision health, mostly with a focus on genomics. The highest degree of public participation was reached through the citizen forum, that represents a way to create practical policy output with involvement of citizens, experts, stakeholders and policymakers (Horgan et al, 2022[26]).

A key contribution in the definition of the best working model of citizen engagement will be gained from the results of a large EU survey on citizens' knowledge and attitudes towards personalised medicine and the use, sharing and integration into clinical practice of genetic and non-genetic healthcare and lifestyle data, that will be distributed within the ExACT project by the end of 2021. In fact, when it comes to citizen perspectives in genome data sharing, we have very limited evidence . The latest report available is a cross-sectional online survey that collected responses from representative publics in the USA, Canada, UK and Australia in 2018 (n = 8967). Results show that participants were most likely to trust their medical doctor and less likely to trust other entities named, and that company researchers were least likely to be trusted. Members of the "high trust" class were more likely to be under 50 years, male, with children, hold religious beliefs, have personal experience of genetics and be from the USA, and they were most likely to be willing to donate their genomic and health data for clinical and research uses. It is vital in this end to survey EU citizens whose trust towards science in general might have changed during the pandemic

4.5 Direct-to-consumer genetic testing

In parallel to but beyond the direct scope of 1+MG, citizens have been able to access their health-related genomic information outside of clinical or research settings, through commercially available direct-to-consumer genetic testing (DTC-GT) services for more than a decade. It is important to take account of this trend in the context of 1+MG. It could offer complementarities to - or even carry the potential for conflicts with - the goal of making available genomic data for research, healthcare and policy development. It also provides an opportunity for some synergies to the goals of 1+MG, in terms of widening buy-in on ELSI provisions and development of trust and education among a wider range of stakeholders. Together with the emergence of directly accessible online interpretation services, these offer consumers ever more insights into their genetic characteristics and predispositions towards developing certain diseases. Proponents of DTC-GT argue that it reduces financial and technical barriers to genetic testing and that providing genetic information directly to consumers may lead to improved compliance with advice on healthy behaviours and greater participation in screening (Hogarth & Saukko, 2017[27]). Others contend that the clinical validity of these tests has not yet been established, making their accuracy unknown (Nordgren & Juengst, 2009[28]; Hogarth & Saukko, 2017[29]). Moreover, unless regulated otherwise, direct to consumer testing bypasses the health sector and the involvement of health professionals, which reduces opportunities for counselling if positive results are received. Health-related DTC-GT can currently be ordered either by a health care provider, or in some cases without any involvement of medical professionals. In the latter case, DT-CGT (e.g. a

[26] https://www.mdpi.com/1660-4601/19/3/1674
[27] https://www.tandfonline.com/doi/full/10.1080/14636778.2017.1354692
[28] https://www.tandfonline.com/doi/full/10.1080/14636770902901595
[29] https://www.tandfonline.com/doi/full/10.1080/14636778.2017.1354692

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testing kit) is often ordered by consumers online. Subsequently, the consumer submits a biological sample (saliva or hair) to the commercial company for DNA to be extracted from it and analysed. In return, the consumer is provided with a test result, usually via a website or email. A systematic review, conducted as part of the Innovative Partnership for Action Against Cancer – Joint Action (iPAAC JA), reported that European citizens have an overall low level of knowledge on DTC-GT, but a high interest in its purchase, mainly to find out their risk predisposition to common diseases, such as cancer, cardiovascular diseases or diabetes. However, the European citizens group has raised concerns about data privacy, data sharing and test result confidentiality and reliability, concerns shared by many clinicians and policy-makers (Hoxhaj, Stojanovic & Boccia, 2020[30]). On the one hand, DTC-GT can in theory support greater access to genetic testing and allow consumers to make healthy lifestyle decisions and control the use of their genomic data. On the other hand, the frequent absence of medical supervision and genetic counselling raises concerns around the misinterpretation of test results, which may, contrary to the original goal, lead to misinformed decision making or demands for follow-up action by the health system (Finlay, 2017[31]). Other concerns relate to issues such as clinical validity and the utility of DTC-GT, protection of minors, implications for donor conception as anonymity can be less guaranteed in countries where this is provided, data sharing, ownership of genomic data and implications for use outside of healthcare, such as in forensics. In Europe, there is currently no common legal framework specifically targeting DTC-GT (Hoxhaj et al., 2020[32]). There are, however, consumer protection laws and more specific laws on In-Vitro Diagnostic (IVD) devices affecting and influencing the regulation of DTC-GT at the EU level.

3.4 Area for consideration

- Secure stakeholders buy-in on technical and ELSI provisions
- Pursue development of trust among a wider range of stakeholders than just citizens
- Deploy information and education customised to each public

5. The multiple stakeholders, and support for trust

Earning and retaining the trust of a broad range of stakeholders will be essential for data sharing in genomics and health. This can be achieved, but will require robust frameworks, and broad participation of different stakeholders from distinct national contexts and with diverse cultural backgrounds in the development of these policies. It will require attention to patient organisations and citizens, where there is some recognition of the merits of data-sharing, subject to appropriate conditions on issues such as consent, governance, privacy protection and feedback on data-use. As the European Patients' Forum puts it through the Chain of Trust project [33], "The right balance needs to be reached between ensuring confidentiality of data while allowing their availability and sharing for public health, healthcare and research purposes." So it is crucial that citizens, patient organisations and data donors from every country are clearly

[30] https://preview.academic.oup.com/eurpub/advance-article-abstract/doi/10.1093/eurpub/ckz246/5828326?redirectedFrom=fulltext
[31] https://www.tandfonline.com/doi/full/10.1080/14636778.2017.1351873
[32] https://pubmed.ncbi.nlm.nih.gov/31923586/
[33] https://www.eu-patient.eu/globalassets/projects/chainoftrust/epf-report-web.pdf

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aware of the meaning and implications of sharing their health and genomic data and of possible benefits.

Among clinicians, the CPME stresses[34] the importance of patients' rights being at the core of its members' work, alongside professional practice, and recognises that patient empowerment requires an informed patient. It sees health literacy as a way of equipping citizens and patients to play a role at the centre of health and healthcare, and it has long been a member of the Strategic Programme Board of the Centre for Empowering Patients and the Communities of the Health Literacy Coalition in Europe. Awareness and education of multidisciplinary health professionals[35], including medical doctors, pharmacists, biomedical specialists, informaticians, data scientists and others, is fundamental for the implementation of the initiative in healthcare systems.

Medicines authorities across Europe have moved at varying speeds to take account of their external stakeholders. The European Medicines Agency (EMA) has been actively interacting with patients since the creation of the Agency in 1995, and it subsequently extended cooperation to include Patients' and Consumers' Working Groups[36] with an interest in medicines, so that these stakeholder groups could bring a 'real-life' experience as well as specific knowledge and expertise to scientific discussions on medicines and on the impact of regulatory decisions. EMA says collaborating with these groups – at all levels from the management board downwards - supports transparency and improves regulatory processes. Nonetheless, EMA has faced repeated demands for greater transparency over its decision-making, and – in response to repeated calls from the European Parliament and health activists, and at the urging of the European Ombudsman[37] – it has progressively opened itself and its data up to closer scrutiny.

As the most representative organisation of Health Technology Assessment (HTA) bodies in Europe, EUnetHTA provides an access point for communication with stakeholders[38] "to promote transparency, objectivity, independence of expertise, fairness of procedure and appropriate stakeholder consultations." More generally, HTA bodies are working on how to effectively share knowledge between those developing and those using technologies. Payers, whether government departments or independent insurers, increasingly display the need to justify their decisions in limiting or authorising expenditure on healthcare delivery, conscious of the often conflicting public pressures on them both to meet demand for new therapies and to exercise financial prudence. But innovative driven healthcare in the genomic era will require them to evolve to become actors in contributing to a framework of cooperation at European level in supporting new approaches to care.

The many bodies that represent the healthcare industries - diagnostic, pharmaceutical, or ICT – are sedulous in their insistence on the priority of people in their strategies. The importance of their role in data generation cannot be overstated. EFPIA runs a Patient Think Tank[39] and is involved in multi-stakeholder collaborations such as IMI PARADIGM[40], as well as supporting its members in delivering their own patient engagement activities. EFPIA endorses "open and

[34] https://www.cpme.eu/policy/professional-practice-and-patients-rights/
[35] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4795240/
[36] https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/patients-consumers-working-party
[37] https://www.ema.europa.eu/en/news/ema-takes-note-european-ombudsmans-decision-pre-submission-activities
[38] https://www.eunethta.eu/about-eunethta/our-network/
[39] https://www.efpia.eu/relationships-code/patient-organisations/efpia-patient-think-tank/
[40] https://www.efpia.eu/relationships-code/patient-organisations/efpia-patient-think-tank/

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transparent dialogue between patients and industry" so the patient perspective becomes an integral part of how medicines are researched, developed and delivered to patients.

National policy-makers and decision-makers, whether politicians or officials, will have a crucial role in the extent to which a genome and health data-sharing framework becomes embedded in healthcare and research systems across Europe and beyond. Some interesting examples in organised cooperation include Genomics England[41] and the National Health System in the UK, FinnGen[42] and the Estonian Genome Center[43]. And already some member states operate voluntary coordination mechanisms of national, regional and local public authorities to link ongoing genomic medicine initiatives into their health services, and are building trust in them, although some of these national exercises are marked by variability, even fragmentation. Greater systemisation at national level would still not attain the ultimate objective of data sharing, which requires the bigger leap from national to EU-level (and ultimately, perhaps, even more international) cooperation and standardisation.

Key infrastructure bodies must work with other stakeholders to agree on standardisation of elements such as sequencing and ELSI-compliant standards to build confidence, as well as ensuring interoperability of health data both within each country and across borders and facilitating the creation of registries. For example, BBMRI-ERIC operates a stakeholder forum[44] as an interface for European patients' organisations, civil society, industry and academia to interact with the biobanking universe and to contribute to the decision-making process, and the role of stakeholders is enshrined in the BBMRI-ERIC statutes. The relationship is intended to increase mutual awareness on needs and expectations on issues related to biobanking, such as data protection, informed consent in health research, health research priorities, and other issues.

EU joint actions also have a role –as in the European Joint Programme on Rare Diseases (EJP RD)[45]. It involves patient representatives at all levels of its work and governance. It also supports Patient Leaderships training developed by Eurordis to empower patient advocates to be valued and equal partners when engaging with diverse stakeholders including healthcare providers, funders or policy makers. It has published a guide to encourage partnerships in rare diseases research projects between scientists and patient organisations ("Collaboration requires an effort from both sides. The more we understood each other's goals, the better the communication and the collaboration became," said one of its authors.) The European Reference Networks include Patient Engagement Groups (ePAGs) giving patients active participation. IMI projects that impact on data exchange also have an indirect impact.

6. Bridging the multiple push/pull factors

All stakeholders have a role to play, although they are by their nature subject to different push/pull factors and working from different value propositions.

But they can all see the same objective in genomic medicine, and the most evident need is for all these stakeholders to recognise the commonality of their cause and work together across the

[41] https://www.genomicsengland.co.uk/
[42] https://www.finngen.fi/en
[43] https://genomics.ut.ee/en/about-us/estonian-genome-centre
[44] https://www.bbmri-eric.eu/stakeholder-forum/
[45] https://www.ejprarediseases.org/

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traditional silos and national boundaries that have inhibited healthcare cooperation in so many ways for so long.

Researchers, clinicians, industry and health care providers will need to share their expertise to create an entire and sustainable translational pipeline, and to facilitate sustainable private involvement and public-private collaboration. Each will have to make its own assessment of the value of collaboration, and of aligning with the interests of other stakeholders, since there is no one-size-fits-all in securing public trust, and no single system of governance that can ensure citizen engagement.

The appropriate protection of personal data is of course essential, but the current context, where people's lives are at stake in the Covid crisis, suggests that some further nuances might now be considered in managing that protection. Citizen engagement in combating the pandemic – whether through observing preventive measures, accepting mass testing, or embracing vaccination - indicates that a readiness exists to act in the general as well as the individual interest. With the additional opportunities around genomes and genomic testing, this might actually be an opportunity to explore whether European citizens are happy with the current situation where data protection prevents some meaningful measures for use of data to fight a global pandemic. An engaged discussion on this issue in the light of so many people being affected by the crisis might throw new light on the conventional questions and answers – and might even have implications on a wider level for other diseases. With the advance of science and technology and the evident risks from new health threats, it may be a moment for the community to review the lines on reasonable and necessary data protection. vs trying to save European's lives.

The way ahead must be stepwise, and success lies in achieving the best balance at any given juncture with existing procedures. Ideally there should be a balance, since responsible use of data is key to good science. The issue is how best to do it.

6.1 Area for considerations

- Establish robust frameworks to maintain cooperation among diverse actors
- Build coalitions with sympathetic health and research organisations
- Promote a sense of joint enterprise among all stakeholders to overcome siloes

7. The need for Action

As the genomics field develops, it is increasingly important for action to be taken now to ensure trust and standards exist in a robust infrastructure. In this way it will also be possible to avoid the creation of siloed platforms that impede the exploitation of data and information.

Researchers, clinicians and health care providers will need to share their expertise. Although some of the required infrastructure and policies are in development, most have not yet been put into practise or established at a scale to deal with millions of individuals' data.

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7.1 Stakeholder Coordination Group

This is the logic behind the creation of a Stakeholder Coordination Group within B1MG to support the 1+MG, to gather input from all stakeholders to feed into achieving the project's objectives.

At its best, it will do more than that: it will have a two-way role in which it develops use cases to demonstrate the benefit for stakeholders involved in data contribution, providing regular and transparent feedback to citizens – the general public as well as patient organisations. The work will be complemented by annual open summits that offer all stakeholders an opportunity to contribute.

Stakeholder representatives will be involved in a consultative manner with the definition of recommendations on resolving the regulatory, policy and legal barriers for cross-border data sharing, on ensuring high data quality standards in line with FAIR requirements[46], and on the infrastructure that will support cross-border access to personalised data in compliance with applicable regulations. This will be based on the requested input from the Working Groups/Working Packages of the 1+MG/B1MG. To ensure stakeholders' engagement (like EJP RD) should be reflected in a collaborative manner, and 1+MG and EJPRD would be expected to learn from each other.

The structured interaction of EJPRD at with international, EU and national/regional level has the potential to support at scale recommendations stemming from 1+MG work, as does its outreach to funders, policy makers, research community, healthcare providers, EU infrastructures and patient. The work done by EJPRD around federated, FAIR and sustainable platforms of data, tools and resources could be a direct input to the 1+MG work, in line with the collaborative work and first POC/use case already started. To ensure alignment and mutual support, EJPRD General Assembly validated direct involvement of 1+MG representative(s) in EJPRD Executive Committee meetings and Policy meetings.

Coordination will extend to individuals and organisations around the globe who need to be alerted to outputs from the 1+MG/B1MG. Amongst the stakeholders, the agenda will explore frameworks for public-private involvement and increased literacy in personalised health. It will also consider future-proofing, so that emerging health technologies can be integrated into healthcare systems. And it will identify future mechanisms of cooperation between stakeholders within the EU and beyond.

A stakeholder portal[47] will deliver tools and support the defining of workflows that can support de-risking and improve the flow of data generation and integration towards patients and the population at large by assisting member states in easing cross-border barriers and developing operational pipelines that can help integrate genomic and health data.

The Stakeholder coordination group will also ensure that governance issues as requested by the respective Working Groups/Working Packages of the 1+MG/B1MG, are appropriately discussed with all stakeholders, where the engagement of ELSI experts will help consolidate knowledge, experience and guidelines, as a starting point for a ELSI framework under which data can be successfully pooled across Europe with adequate standards and quality for sequencing and phenotypic and clinical data to command trust.

[46] https://www.nature.com/articles/sdata201618
[47] https://sites.google.com/ebi.ac.uk/b1mg-stakeholders-portal/home

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The B1MG/1+MG will organise workshops and country exchange visits to improve understanding of the standards, indicators, and review processes, and promote capacity building in the use of genomic data in healthcare.

There are challenging issues to resolve: the values and ethics underpinning a pan-European framework; agreement of a governance model of contractual arrangements on data use and data inclusion; processes to govern data access; and clarification of aspects of the General Data Protection Regulation relating to consent, privacy, and research uses of genomic data in the different member states.

It is not only a clear system for data governance that is needed to build trust. There is also a need for adequate infrastructure, and for education – which must take account of the fact that while patients may have a vested interest in data sharing, this is less the case for the general public, and may require a differentiated communications strategy. Health literacy has a potential role in improving community empowerment – although that will require capacity building among citizens and attention to the quality of information provided

7.2 Areas for Consideration

- Adjust speed of action to match the growing speed of scientific possibilities
- Involve stakeholders in generation of recommendations
- Ensure virtuous feedback loops to maintain and increase stakeholder buy-in

8. Conclusion

The destination is to ensure that all citizens and patients have appropriate best quality of care. In building towards that tomorrow, it will be vital to make sure that all stakeholders, top down and bottom up, know what is recommended, and why.

1+MG offers a facility to help turn this aspiration into a reality. It provides both hard data at an unprecedented scale, and a model of engagement that – properly deployed – can build, maintain and reinforce trust among the public and the public health authorities in the merits not just of 1+MG but of the concept of the collection and exchange of citizens' data. This project provides both a testbed and a delivery vehicle for how to ensure that citizens' concerns receive priority attention, while solutions are found to the myriad technical, scientific, legal and political issues that the project also raises. To carry through on this goal, the requirements will range from investment

The requirements will range from investment in human and technical infrastructure capacity to collaboration among all stakeholders to creating an adequate framework.

Ultimately, the success or failure of the project will depend on how far it is possible to create an institutional climate which is receptive to change and which empowers health care organisations and professionals to accommodate the evolving expectations of the community. There is no need to wait for tomorrow to start those preparations. The example of the European Parliament's resolution on strengthening action against cancer and in the plans for the

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forthcoming EHDS show that these issues are rising up the institutional agenda. They represent some progress. But many more efforts should also start now.

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