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Germline genomic medicine: A BigMed needs analysis

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Author
DNV GL, Group Technology and Research (GTR), Precision Medicine Program

Contact
Sharmini Alagaratnam
Principal researcher, Precision Medicine Program,
DNV GL Group Technology and Research (GTR)
E-mail: sharmini.alagaratnam@dnvgl.com
Mobile +47 9937 1772

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Disclaimer
The needs detailed in this white paper are for general illustrative and information purposes only, and do not represent professional or legal advice of any kind.
See Section 3 methods for a full description of how these needs were gathered and processed for presentation here.

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DEFINITIONS

Genomic medicine	The medical discipline that uses genomic information about an individual generated by whole exome or genome sequencing as part of their clinical care (e.g. for diagnostic or therapeutic decision-making), and the health outcomes and policy implications of that clinical use.
Incidental findings	Findings outside the original purpose of testing that are not actively sought out but identified.
Reanalysis	A process through which original, intermediate or derivative data and/or biological samples from exome or genome sequencing are reassessed, usually in the event of new technologies or medical knowledge that may impact patient management becoming available.
Secondary findings	Findings outside the original purpose of testing that are actively sought out and/ or analysed.

CONTENTS

EXECUTIVE SUMMARY

Genomic medicine, or the use of genomic information about an individual as part of their clinical care for diagnostic or therapeutic decision-making, has a specific and essential need to compare genetic variants found in each new patient to those already observed and evaluated in previous patients nationally and internationally for best effect. This transformative model puts complex technical, organizational, ethical and legal demands on current healthcare systems, challenging the effective implementation of genomic medicine.

Work Package 3 in the BigMed project focuses on making germline genomic data available and actionable, where as part of this scope, a **needs analysis for germline genomic medicine** at Oslo University Hospital (OUS) was performed, with a perspective up to 10 years from today. A systems-oriented analysis of the insights gained from the interviews was performed, resulting in the five categories of needs summarized in the figure on the opposite page.

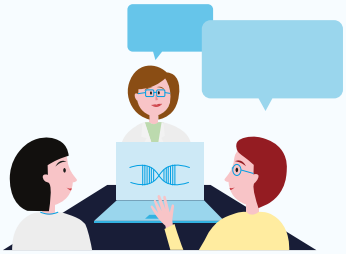
Selected national and international genomics initiatives and strategies, existing national and international guidelines, and standards and recommendations were also examined for tools, approaches and methods that responded to the needs described. These resources illustrate the different approaches being explored globally to effectively deliver genomic medicine.

This paper takes the perspective of genomic medicine as a microcosm of a learning healthcare system, where the digitalization of healthcare enables safe and effective (re)use of knowledge from one patient to treat the next; effectively closing the loop on real world clinical data. Through this analysis key needs are identified and presented that a technical, organizational and legal blueprint for future genomic medicine would ideally respond to.

Categories of needs for germline genomic medicine

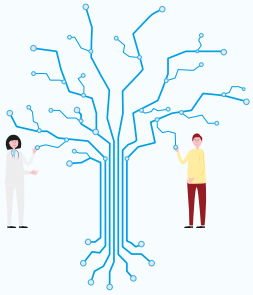
PATIENT COMMUNICATION

- Efficient identification and enrolment of eligible individuals
- Quality information on genetic testing
- Standardized dynamic consent management
- Return of results
- Active patient collaboration
- Ripple effects on potentially affected family members



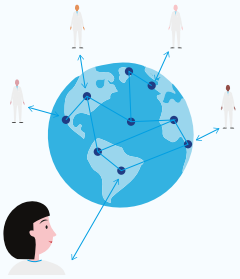
COLLABORATIVE WORKING MODELS

- Integrated clinical genomics workflow
- Initial patient characterization and test selection
- Interpretation and reporting of results



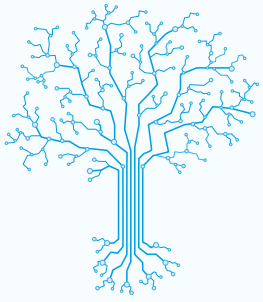
DYNAMIC INFRASTRUCTURE, KNOWLEDGE AND PATIENT MANAGEMENT SYSTEMS

- Dynamic infrastructure management
- Dynamic knowledge curation
- Dynamic management of clinical genomics patients



RECIPROCAL KNOWLEDGE AND DATA SHARING

- For current and future patients
- To build global knowledge bases
- Secondary use of data for research



FUTURE CHALLENGES

- New patient groups and new uses
- Increased volume and complexity of information sources

INTRODUCTION

Genomic medicine, defined here as use of genomic information about an individual generated by whole exome or genome sequencing as part of their clinical care for diagnostic or therapeutic decision-making, is undergoing rapid transition from research into mainstream healthcare.

Current models indicate that the proportion of genomes being funded by healthcare globally will move from 20% in 2017 to over 80% in 2022, with over 100 million genomes being sequenced by 2025 [1]. Yet the transformative character of genomic medicine puts complex technical, organizational, ethical and legal demands on current healthcare systems.

Genomic medicine has a specific and essential need to compare genetic variants found in each new patient to those already observed and evaluated in previous patients for best effect. Genetic variants cannot be accurately interpreted in isolation, but set in the context of global genetic knowledge they can used to diagnose patients both more accurately and more quickly than has been previously possible.

Figure 1 shows the ideas scenario for flow of information for genomic medicine in Norway developed for this paper and as a part of the BigMed project, where clinical decisions in a specific hospital are made for a single patient by comparing that individual's genomic data to knowledge gained from patients at other hospitals in Norway and internationally, either directly or by querying curated knowledge bases based on clinical and research resources. Should it be relevant, the patient's data is used for reanalysis at a later time point. Similarly, clinical genomics units at other hospitals can query the first hospital when diagnosing or treating their patients. Research efforts can also contribute to this space, and genomic data from healthcare is already being made available and proving valuable to industry.

This working model greatly challenges current organizational and legal frameworks controlling healthcare data sharing, resulting in a range of barriers preventing the effective implementation of genomic medicine [2]. Work Package 3 in the BigMed project focuses on making germline genomic data available and actionable, where as part of this scope, **a needs analysis for germline genomic medicine** at Oslo University Hospital (OUS) was performed.

> "No one country can possibly teach us everything we need to know about human genetic disease."
>
> **Eric Lander,** founding director of The Broad Institute, at the 7th Plenary meeting of the Global Alliance for Genomics and Health, Boston, November 2019.

Flow, use and sharing of data in genomic medicine: an ideal scenario.

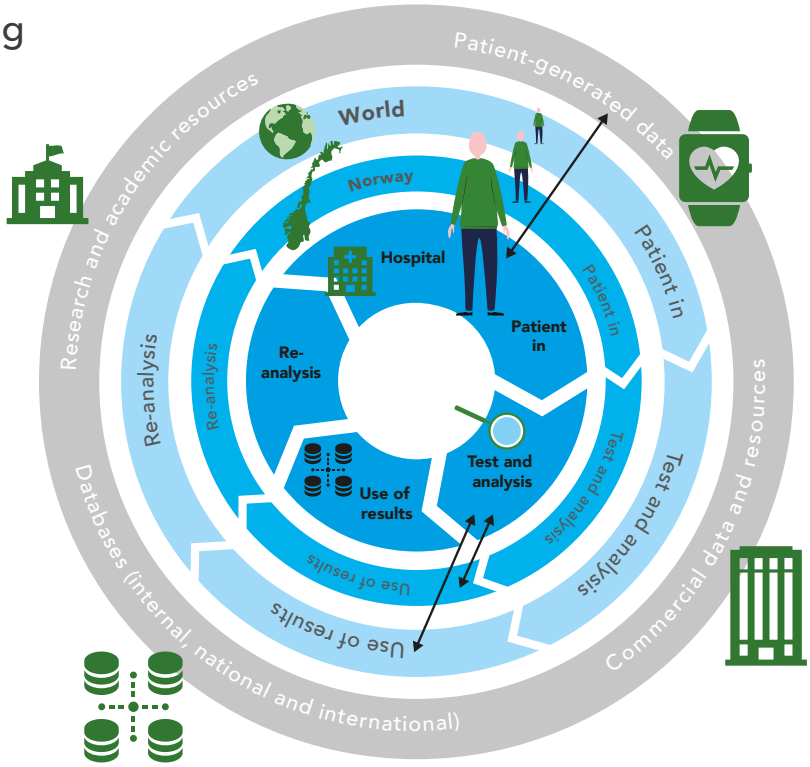


Figure 1: Patients entering the genomic medicine pathway reciprocally rely on knowledge gained from patients within the same hospital but also other healthcare providers nationally and internationally for their diagnosis and management. At the same time, genomic medicine providers interact with multiple resources within a larger ecosystem including research databases, commercial providers and patient-generated data.

A series of semi-structured interviews was carried out with individuals representing units that deliver genomic medicine today as well as units that expect to do so in the near future, located both at and associated with OUS. A systems-oriented analysis of the insights gained from the interviews was performed, where the **five categories of needs that emerged from this exercise are presented in this paper**.

This work takes the future perspective of genomic medicine as a microcosm of a learning healthcare system, where the digitalization of healthcare enables safe and effective (re) use of knowledge from one patient to treat the next. This white paper also includes a non-exhaustive review of national and international genomics initiatives, mapping relevant existing approaches and solutions to the needs identified through this work, and seeking out commonalities where possible. This paper is not meant to describe technical, legal or organizational compliance solutions as a blueprint for future genomic medicine, but rather to list in a structured manner the key needs that such a blueprint would ideally respond to.

The genomic medicine paradigm shift challenges many aspects of healthcare, from technical, legal and organizational, to ethics and reimbursement models, where there is a growing impetus to respond to the needs identified and presented in this paper in order to provide accurate and timely care to patients.

METHODS

Current and future needs related to genomic medicine at OUS were gathered through a series of eleven interviews.

Informants included individuals from units currently delivering healthcare and associated research and services through genomic medicine at OUS, as well as units who expect to offer genome sequencing to their patients in the near future. Areas of responsibility include clinical, laboratory and computing infrastructure services for rare disease, cardiac genetic and hereditary cancer diagnostics, with newborn screening and childhood cancers as future areas of application for genomic medicine. Respondents were asked to describe their needs within their area of responsibility in genomic medicine from today and up to a 10-year timeframe. Insights from the interviews were extracted and analyzed by iteratively grouping these to identify central and common needs themes.

In order to understand which tools and guidance are currently available that respond to the needs identified in this work, relevant recommendations, guidelines, policies and best practices for governance and technical standards were reviewed and mapped to the need themes identified.

In an associated exercise, the following national and international genomic medicine initiatives were then examined to extract and map approaches, tools and solutions that are either already available, in development or identified as future focus areas and that respond to the need themes identified: Genomics England, Australian Genomics, as well as the national genomics strategies for Norway, Denmark, Sweden and Finland.

CATEGORIES OF NEEDS FOR GERMLINE GENOMIC MEDICINE

Analysis and grouping of insights obtained through the interviews performed produced five central categories reflecting groups of needs. These are presented and discussed below in the context of the specific findings from which they arose.

1. Patient communication

Taking the individual to receive clinical genomic sequencing as a starting point, this category collects needs relating to the patient pathway including their enrolment, patient education and information, the consent process, the receipt of results and their role in the process, as well as ripple effects for potentially affected family members. In general, many of these processes would benefit from a move to continuous dialogue as a means of communication as opposed to a series of single encounters with limited opportunity for returning with questions or more information.

1.1 EFFICIENT IDENTIFICATION AND ENROLMENT OF ELIGIBLE INDIVIDUALS

Genomic medicine serves individuals eligible for clinical genomics who may be either symptomatic (such as rare disease patients), pre-symptomatic (such as family members of these patients, or individuals who may have a genetic cause or predisposition to a health condition) or asymptomatic (family members with carrier status). In both cases, eligibility criteria need to be clearly defined, accompanied by efficient and equitable systems and processes that facilitate the identification of eligible individuals, and allow timely enrolment of requisitioning and for appropriate testing.

1.2 QUALITY-ASSURED INFORMATION ON GENETIC TESTING

Upon offering clinical sequencing, individuals need to be provided with quality-assured and standardized information packages on the test to be performed and what kinds of results they can expect to receive, directly through genetic counselling and indirectly through

supporting materials. Uncertain (for example Variants of Uncertain (clinical) Significance, VUS), incidental and secondary findings (see table at the start of this report for definitions of these terms) that may be the outcome of clinical genomics all require special attention, informed by institutional policy and patient wishes. Any potential sharing and further use of the patient's personal data, either for their own benefit, for that of other patients, or for research, needs should ideally be clearly communicated and consented to (see section 1.3). Finally, communication methods and processes that promote continuous dialogue between the individual and the healthcare institution as needs arise need to be considered, as an alternative to a single interaction moment.

1.3 STANDARDIZED DYNAMIC CONSENT MANAGEMENT

Clinical genomics diverges from other clinical testing, where the results from the latter represent single timepoint snapshots. In contrast, the results of clinical genomics test are analyzed within a rapidly evolving landscape of medical knowledge, and may be relevant for the entire lifetime of a patient. For example, genetic testing of a patient which does not provide a clear, clinically actionable result may provide one after reanalysis in the future, when more is known about genetic disease. Accumulation of new knowledge induces constantly evolving needs for use of an individual's genome data. Currently, genetic testing in Norway is specifically legislated by the Biotechnology Act of 2003, and draws a line between genetic testing for diagnostic purposes and for pre-symptomatic, predictive and/or for carrier status, where for the latter written consent and genetic counseling is required. However, a diagnostic test by exome/genome sequencing may also reveal pre-symptomatic, predictive, and / or carrier conditions, raising the question of if it is the purpose or the findings of a test that determines how it is categorized (and which requirements apply). Current interpretation defines a test's findings to be decisive of if a test is categorized as predictive or diagnostic. However categorizing tests by their purpose can also be advocated for, where legislative changes in the current Biotechnology Act of 2003 supporting this approach are currently under review by the Norwegian Ministry of Health and Care Services.

The fundamental need for data sharing that enables comparison of patients undergoing clinical genomics (see Introduction), and the reuse of data for purposes including those described at the start of Section 1.3. all additionally impinge on the categorization of a test at its outset, where clarity around the legal requirements will affect the implementation of dynamic consent.

The needs gathering interviews and analysis performed for this paper specifically suggested consent as one possible legal rationale for data sharing. Using dynamic consent as a basis for communication around patient preferences would enable a continuous dialogue as opposed to decisions made at a single time point that in practice are difficult for the patient to change. A clear distinction needs to be made with regard to an individual's consent for the use of the data for their own benefit, for the benefit of other, future patients and for research purposes. Where possible, healthcare institutions need to develop policies and standardize the content and process of consenting across all clinical pathways where genome sequencing is performed.

A parallel BigMed activity and white paper [3] addresses consent needs in clinical genomics more in depth, including issues related to incidental and secondary findings, and ripple effects on biologically-related family members.

1.4 RETURN OF RESULTS

Upon the return of results, individuals need accurate understanding of and access to documentation on test findings and the data used to generate it, ideally tailored to their needs from professionals who are specially

trained to return clinical genomics results. They also need recourse to resources who can respond appropriately to questions they may have after the initial return of results.

1.5 ACTIVE PATIENT COLLABORATION

Accurate information about and often from the individual about their condition is crucial for reaching the correct diagnosis. The amount and accuracy of patient-derived data would be improved if patients could contribute dynamically with information when appropriate, as opposed to input at a single timepoint. As individuals become more aware and involved in their own healthcare, there is an opportunity to recognize and potentially incentivize them to collaborate more actively in both their own health, as well as to build new health knowledge through research efforts. One example of this could be the inclusion of reporting of phenotypes by the patients themselves, as opposed to exclusively clinician-reported phenotypes [4].

1.6 RIPPLE EFFECTS ON POTENTIALLY AFFECTED FAMILY MEMBERS

Clinical genomics also differs from other clinical testing in the extent to which it has the potential to affect family members of the individual diagnosed with a genetic condition, from diagnoses of their own or identification of carrier status, to predisposition and prenatal testing. As of today in Norway, all efforts for contacting of potentially affected family members must occur through the index patient (the patient under investigation). Given the far-reaching and potentially serious effects of a genetic finding, more efficient methods and sufficient resources to educate and enable the patient to inform their family members of the finding and its implications should be considered. Alternative approaches for screening and management of select familial diseases than solely through the index patient are worth exploring, where necessary accompanied with appropriate legislative changes.

2. Collaborative working models

The nature of clinical genomics requires close collaboration of the patient-facing clinical unit which gathers, processes and returns phenotypic and other medically relevant information, and the laboratory unit which performs genomic sequencing and interprets genomic data. This has consequences for both general and specific communication and interaction points between these units as discussed below.

2.1 INTEGRATED CLINICAL GENOMICS WORKFLOW

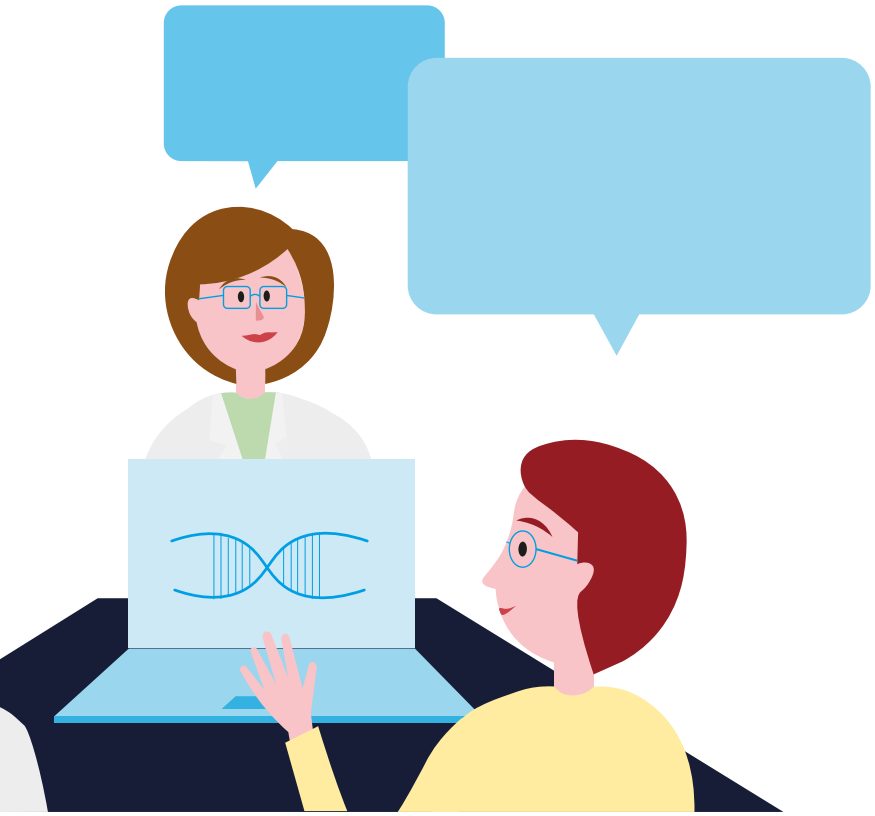
The clinical, laboratory, bioinformatic and IT units represent essential components of the clinical genomics patient pathway. Common communication and collaboration tools and production systems need to support the integration and appropriately controlled availability and flow of relevant information to partners in different disciplines during the diagnostic pathway, while maintaining a clear and logical division of duties. Economies of scale argue for the creation of critical mass in key technical competencies and infrastructure, however effective communication between roles must be ensured. Building competencies across clinical, laboratory, bioinformatic and IT units promotes effective collaboration and is likely to facilitate better communication across the genomics pipeline.

2.2 INITIAL PATIENT CHARACTERIZATION AND TEST SELECTION

Differential diagnoses for rare diseases are enabled by complete and accurate phenotypic data. Accompanying clinical and familial data also provides great value, particularly for diagnosing heritable cancers. Standardized terminologies and ontologies such as the Human Phenotype Ontology or ICD-11 are critical here to document, as well as tools that facilitate their correct use, presentation and integration with other clinical data. Together these can guide the choice of genetic analysis to be performed, for example by informing the selection of relevant gene panel(s). A high level of genetic literacy of the requisitioning clinician is beneficial for the effective clinical use of these vocabularies and tools. Open communication avenues supported by the necessary resources are needed to ensure the correct tests are requisitioned before sequencing is performed, and to convey what kind of and when outcomes can be expected.

2.3 INTERPRETATION AND REPORTING OF RESULTS

The interpretation of findings in a clinical genomics setting and subsequent reporting of results is both complex and challenging. This is particularly true in cases where the analysis results in no findings or where the findings are uncertain. To compound these challenges the reporting of results must sometimes be delivered by clinicians who do not have a high level of genetic literacy. Standardized, quality-assured alternatives to today's report formats need to be considered, which present the results thematically and hierarchically for ease of understanding; as well as transmission methods, where 'live' reports can enable active work with the results and embedding of further references and resources. Finally, there is value to be gained from continued communication between the clinical and laboratory units after the report has been delivered, due to the ever-growing body of knowledge on human genetics (see Sections 3.2 and 3.3).



3. Dynamic infrastructure, knowledge and patient management systems

The relatively recent transition of genomic medicine from research into the clinic means that the knowledge base on which patients are diagnosed and treated is continuously being built upon.

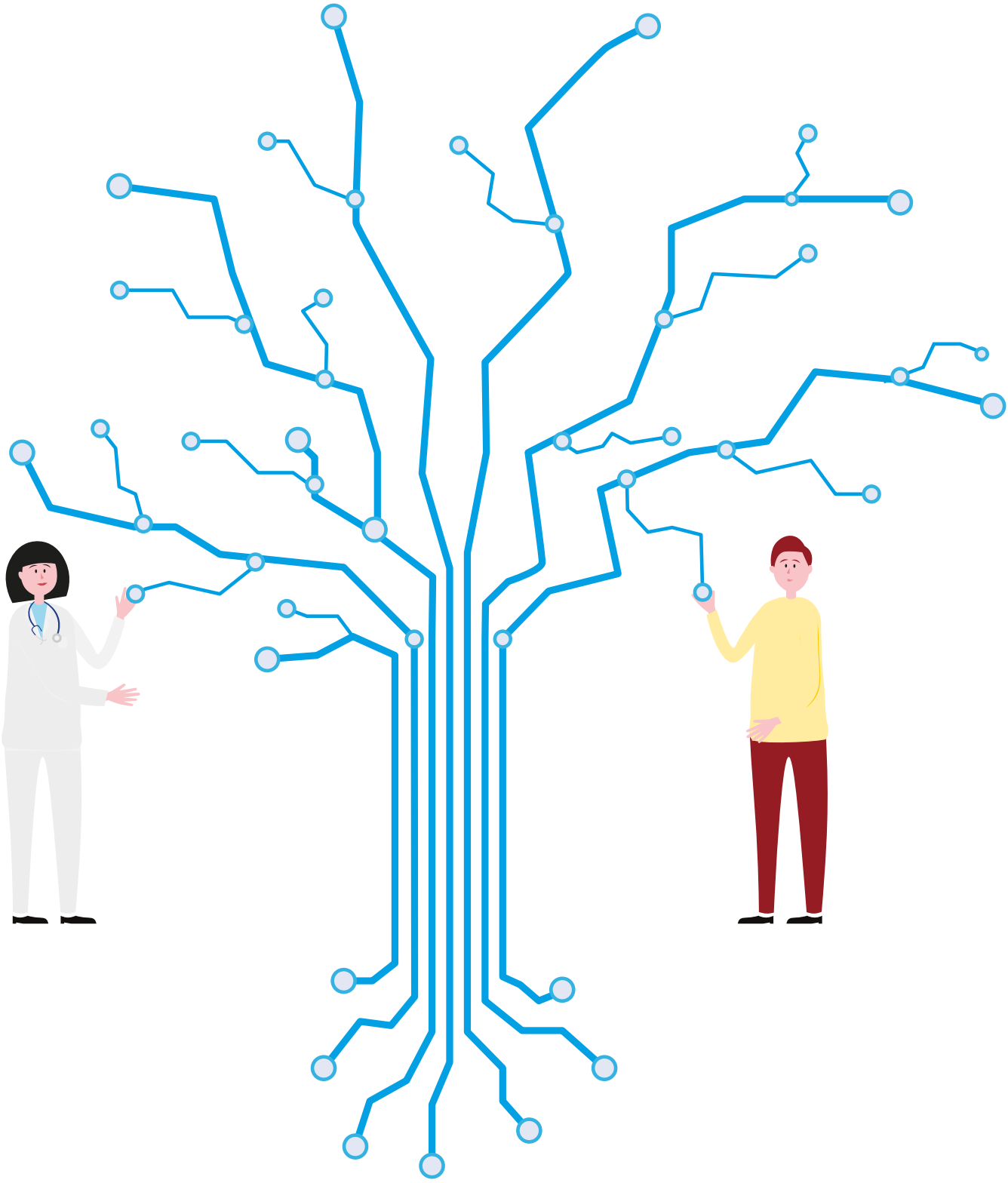
Active use of real-world clinical data enables knowledge gained from diagnosing and/or treating one patient to treat the next similar patient more effectively. In order to offer today's and tomorrow's patients the best level of care, adaptable and scalable infrastructure and management systems are needed to continuously gather, manage and curate the knowledge needed and dynamically interact with the patients for whom this is relevant. The explosive growth of both biomedical knowledge and the number of individuals sequenced will require a high level of automation in these systems to allow continued improvement in accessibility and quality of genomic services.

3.1 DYNAMIC INFRASTRUCTURE MANAGEMENT

The computing infrastructure required to support genomic medicine includes sequencing hardware, laboratory information management systems (LIMS), secure storage and high-performance computing (HPC), integrating a bioinformatic pipeline to analyze the genomic data and clinical decision support software to interpret the output. Due to the rapid development of tools and software in the field, this infrastructure must be more adaptable than in other diagnostic specialties. Similarly, clinical-grade service of this infrastructure requires an innovative and agile service provider capable of offering interoperability among internal and external information systems, 24/7 support, and secure, fast and stable HPC, network and data storage. This infrastructure should support clinical-grade quality and audit processes, including continuous quality monitoring and auditing. There is an additional need for a development or test environment which allows for the testing and performance evaluation of new tools. Where suitable, commercially available products and services should be considered for inclusion in clinical pipelines
.

3.2 DYNAMIC KNOWLEDGE CURATION

At the time of writing, an estimated 200-300 genes per year are being associated with human diseases or traits [5]. The rapid accumulation of knowledge has immediate implications for clinical diagnostics. Firstly, the composition of gene panels for suspected genetic conditions may change rapidly. Secondly, the interpretation and classification of variants relies heavily on this scientific knowledge. Research findings on genes and variants relevant for disease require validation before they can be taken up in a clinical setting. Validated genes, identified through continuous and dynamic curation, can be incor-



porated into existing panels and/or new panels can be developed. Ideally, gene panels and how they are run would be harmonized and standardized nationally or internationally in their content to ensure patients receive the same tests regardless of hospital attended. Information on the genes included in each panel and the clinical evidence for their inclusion need to be readily available to all clinicians who requisition clinical genome sequencing, including new panels when introduced.

Similarly, the process of variant interpretation will continue to require continuous refreshment and updating of the knowledge base upon which these interpretations are performed. Variants of uncertain significance (which can be re-classified when new medical knowledge becomes available) require specific and particular monitoring for changes. However all classified variants – not just those of uncertain significance - are subject to changes in classification and also need to be considered for (automated) monitoring for changes. Finally, sharing and harmonization of a classification and evidence knowledge base nationally is necessary to ensure quality and equal access to all patients regardless of hospital attended.
All these issues will also be relevant for new genomic sequencing methods which give rise to new kinds of genomic information, for example regions outside known gene-coding sequences or structural or copy number variants which may also cause disease and be clinically actionable.

3.3 DYNAMIC MANAGEMENT OF CLINICAL GENOMICS PATIENTS

Incomplete knowledge of all potential gene-disease associations, the relevance of structural and non-coding variants and diagnostic test quality all contribute to today's diagnostic yield for rare disease by clinical genomics of between 30 and 50% [6]. This underlines the urgent need for a systematic and standardized approach to retesting, reanalysis and/or recontacting of patients with no or uncertain findings. Triggers for initiating retesting, reanalysis and/or recontacting may include new or changed medical knowledge (see section 3.2 above), a predefined time limit, as well as new medically relevant information from patients. This would represent a significant change in clinical practice, where clinical, legal, ethical and economic repercussions need to be carefully assessed before moving to such a model. Addressing the automation and scalability of this process may in time mitigate the challenge of vastly growing amounts of knowledge and numbers of patients sequenced.

4. Reciprocal knowledge and data sharing

There are three generalized areas of utility of genetic data, where the fundamental need in genomic medicine for genetic variants to continuously be put in context of prevailing knowledge applies equally to all three. Developments in technology and the use of genetic and associated data necessitates a continuous discussion and consensus on what legally constitutes anonymous and personal data, and independent societal measures for evaluating the international sharing of these data types. This has direct consequences on the legal, infrastructural, security and governance mechanisms required to ensure that knowledge and data is used as intended.

4.1 FOR CURRENT AND FUTURE PATIENTS

For genomic medicine in general, but for rare diseases in particular, there is a need for secure and efficient methods of communicating data from the current patients both nationally and internationally in order to make an accurate diagnosis. The amount of data from a single patient that needs to be shared to be of clinical benefit spans a scale from single genetic variants to a subset of or the whole set of genetic variants specific to that individual, as well as accompanying relevant phenotypic and clinical data. Sharing of this data can occur through direct contact with experts or through reference databases (such as ClinVar and ClinGen) or other patient matching services (such as Beacon, Matchmaker Exchange or GeneMatcher).

The diagnosis of rare diseases and hereditary cancers would benefit from access to national knowledge and reference bases which share specific subsets of data, as opposed to patient data in general. The first steps in this direction have been implemented by solutions that share anonymous variant classifications in Genomics England [7], the Netherlands [8], Canada [9], the Trusted Variant Exchange solution prototyped in BigMed [10] and other knowledge-base software such as the Allele Frequency Community. In combination with reference groups and competence networks for defined (groups of) disorders (see also section 3.2), this would allow for quality control and harmonization across different clinical genetics units nationally and internationally, and ensures that knowledge created within the healthcare system remains accessible for the diagnosis of future patients. Sharing of increasingly larger subsets of clinically-relevant patient data – from attaching specific diagnoses to genetic variants to associated phenotypes, clinical data and fuller sets of personal genomic variation expands the possibilities available for the patient. Finally, continuous assessments on what constitutes anonymous and personal data in the context of genomic medicine will assist in ensuring how and which components and subsets of patients' data can be shared to ensure they get the best quality of care, while maintaining privacy compliance and respecting the individual patient's wishes.

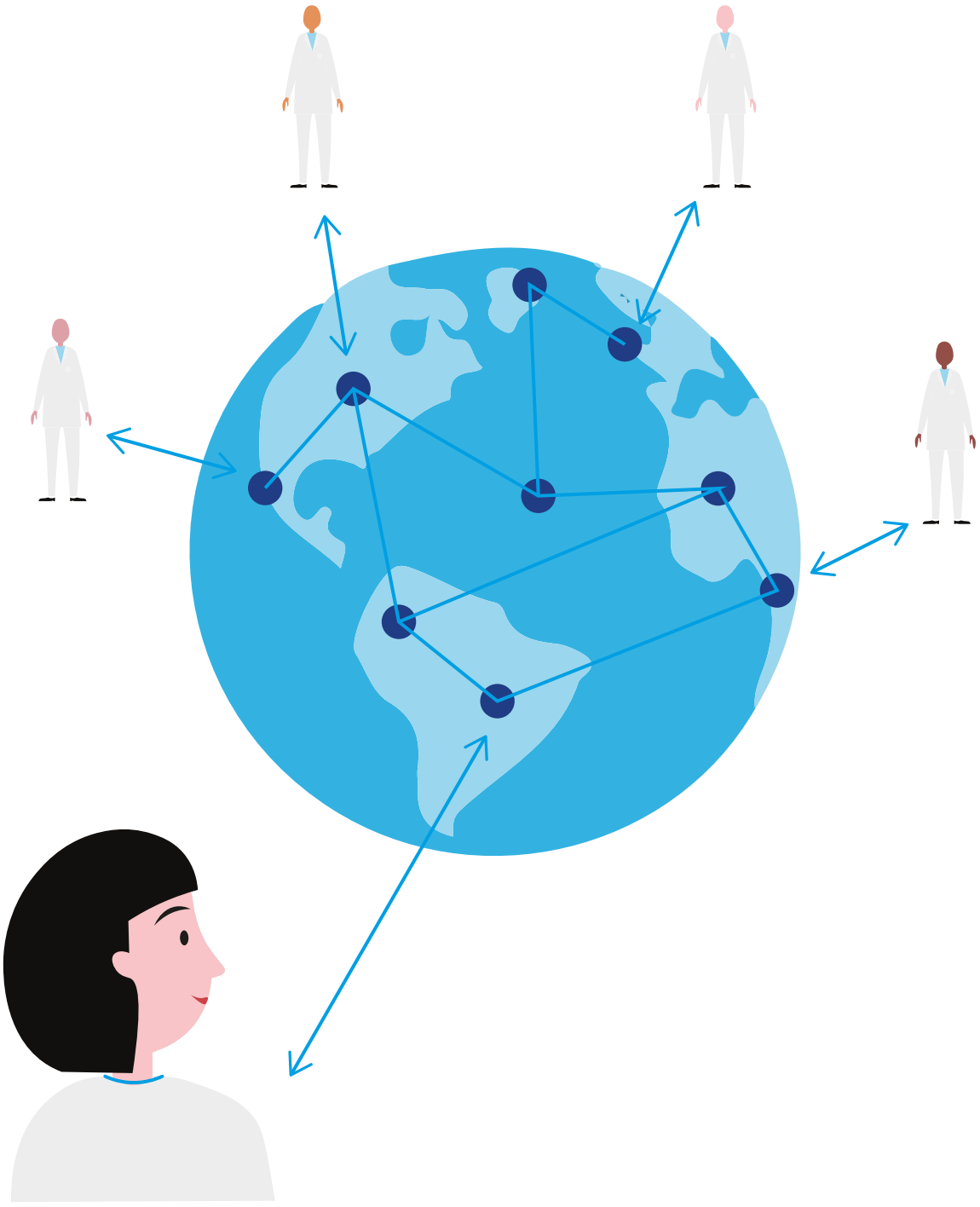
4.2 TO BUILD GLOBAL KNOWLEDGE BASES

Accessing existing international knowledge sources for internal clinical uses has the potential for reciprocal contribution through similar channels, ultimately increasing the quality of global knowledge bases for genomic medicine. Continuous legal clarification on what data can be shared to which cross-border resources is required, supported by technical solutions that both facilitate international data sharing and ensure compliance.

4.3 SECONDARY USE OF DATA FOR RESEARCH

Only a fraction of the genomic data generated clinically is examined for the purpose of diagnosing and/or treating the patient from which it comes. Yet the full dataset may conceivably be examined for additional variants, which in time may prove relevant for the patient's condition. Even more compellingly, the secondary use of genomic and associated data has the potential to expand biomedical knowledge, where collectively genomes sequenced for clinical and research purposes represent an untapped resource for medical and fundamental research. In principle such an approach would allow the development of sufficiently powered cohorts and studies, especially if applied internationally. Clinical decision support tools and eventually algorithms rely on data of sufficient quality and quantity, where both the inclusion of adequate normal controls and small cohorts (for example in childhood cancers) are challenging.

These issues illustrate the difficulties in distinguishing between purely clinical and purely research activities in genomic medicine, with corresponding legal, ethical and financial (reimbursement) impacts. It requires fundamental questions to be answered about if, how and which clinically-generated genomic and associated data is made available for research, and the technical infrastructure required to receive, manage and enable analysis of this data securely and efficiently in a research environment despite its clinical origins. Governance of this data, including accountability and transparency in its use, needs to be in place for the individuals contributing their data for research purposes. Exploration of potential synergies between infrastructural, competence and governance needs for research and clinical genomics may avoid duplication of resources.



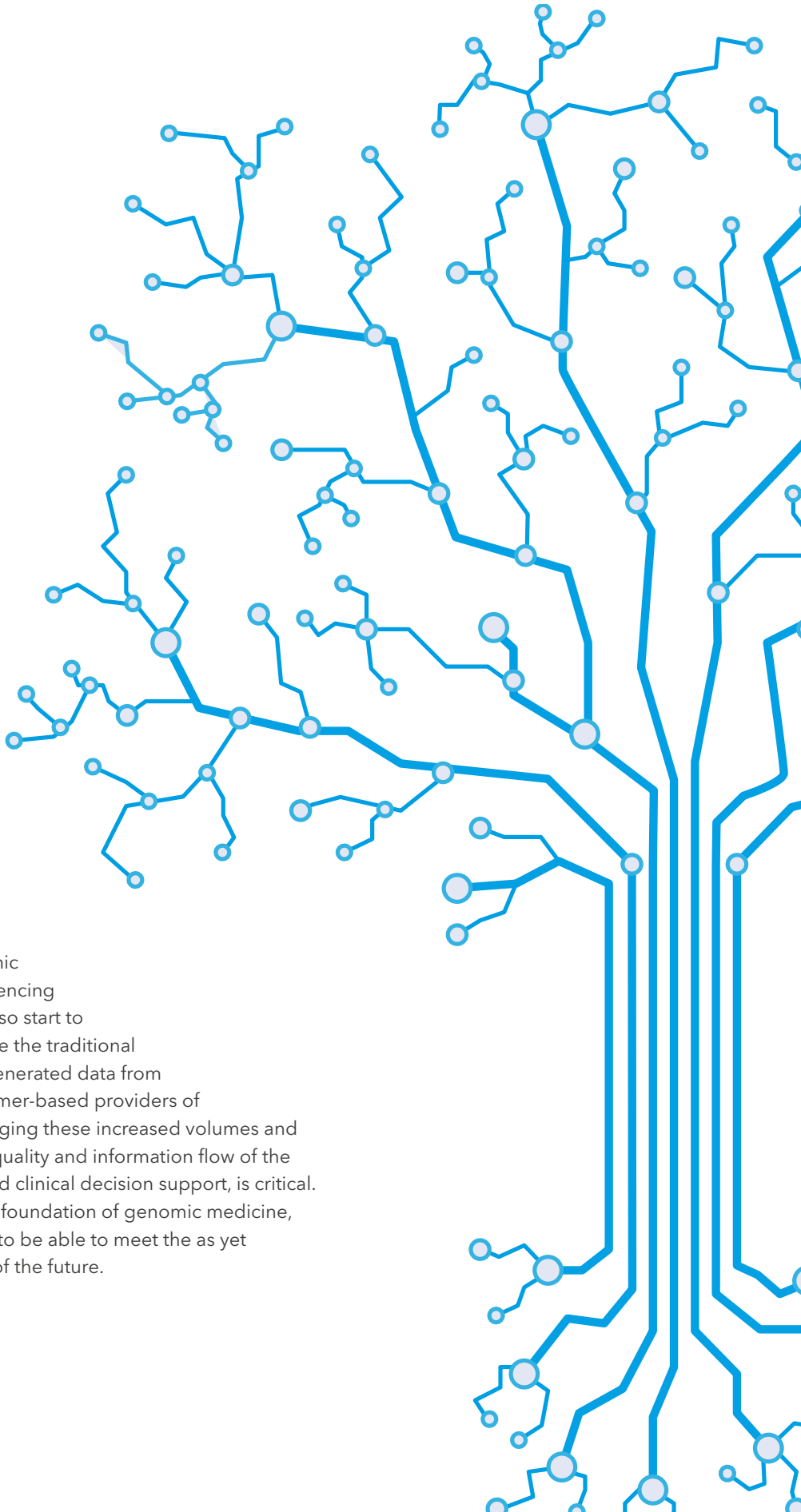
5. Future challenges

The four previous categories described above discuss needs identified for cohorts of patients that are currently being offered clinical genomics, and for the purposes that are known and implemented today. This final category collects needs and challenges for patient cohorts and purposes which are closer to the 10-year perspective as opposed to more immediate needs, and which are expected to be integrated into clinical practice within the next decade, where a summary [11] in a special issue of Genome Medicine summarizes the next-phase challenges and some advances to meet them.

5.1 NEW PATIENT GROUPS AND NEW USES

As new patient groups become relevant for clinical genomics, continuous review on which (sub)cohorts are to be offered genome sequencing will be required, alongside discussions on prioritization and scalability of both hardware and computing storage and power solutions needed to meet the increased volumes of patients (see Section 5.2). Continuous genetic literacy training for clinicians on the applications of genetic testing are needed, as well as uptake and integration of research findings in the clinical setting. New areas of application may have other requirements, for example time-critical genomic analysis for critically ill new-borns. Sequencing of microbes causing infectious diseases may also need to be integrated into clinical trajectories. Germline and somatic genome sequencing are often the remit of different hospital units, yet there are clear opportunities and benefits from considering these results from a single patient together. One example is genome sequencing of tumours which also generates germline genomes which can contribute to strengthening the underlying databases enabling genetic diagnostics.

Additionally, as genetic knowledge increases, new uses of genomics data previously generated for screening, diagnostic or predictive purposes may become relevant and necessary to return to the individual, such as their pharmacogenetic profile or polygenic risk scores for common diseases such as Alzheimers and cardiovascular disease, as well as consequences for family members. The development of such clinical knowledge implies larger scale sharing of genotypes, phenotypes and clinical data from both patient and control groups than occurs today, before these can be fed back and implemented in clinical care. Patients' increased understanding of genetics and its potential may also increase expectations from existing healthcare systems. Taken together, these new needs may point to a need for organizational change within systems, (re)assigning responsibilities to be able to deliver healthcare services in a more patient-centred manner.



5.2 INCREASED VOLUME AND COMPLEXITY OF INFORMATION SOURCES

With technological advances, all indications are that information and data used in the clinical genomics setting will grow tremendously in volume and complexity, further magnifying today's issues. The most immediate change is that from whole exome to whole genome sequencing, but also includes the generation and capture of new data types which can be both phenotypical and/or clinical (such as quantified metabolomics, deep phenotyping and imaging) or genomic (such as RNA and/or long-read sequencing and epigenetic profiles). Data may also start to be incorporated from sources outside the traditional healthcare system, such as patient-generated data from sensors, or indeed from other consumer-based providers of healthcare or genomic data. In managing these increased volumes and sources of data, assessments of the quality and information flow of the data, as well as advanced analysis and clinical decision support, is critical. Modern infrastructure must lie at the foundation of genomic medicine, with built-in scalability and flexibility to be able to meet the as yet unknown needs and developments of the future.

MAPPING OF EXISTING TOOLS AND INITIATIVES TO NEEDS

The current and future needs identified for genomic medicine at OUS described in the previous section are by no means unique to this institution, or Norway. At least 14 countries have launched national genomic medicine initiatives to meet the challenges of clinical implementation, taking and/or combining the following approaches: using genomics at scale to answer real-life clinical questions in rare diseases and cancer; population-based sequencing projects; and building large-scale (centralized or distributed) infrastructure and platforms to support genomic medicine[12].

These national efforts are at different stages of transition into mainstream healthcare, where success is dependent on many country-specific factors including genomic medicine implementation models, funding strategies, healthcare system organization and legislation. Despite this, some learnings can be gleaned from examining the national approaches and strategies taken. For this purpose, a non-exhaustive review was performed of the genomics programmes in England and Australia as examples of programmes with a clear clinical implementation path, as well as the national genomic medicine strategies in Norway, Sweden, Denmark and Finland to ground this work in a national and regional context.

This section maps relevant examples of existing tools, processes and mechanisms identified in these programmes and initiatives to the five need categories identified, as well as relevant international standards, guidelines and recommendations relating to clinical genomics. The results are presented the following series of five figures, each responding to one need category. Existing tools and methods

already in use are presented in orange boxes, and relevant policies, recommendations and guidelines in green boxes. Note that each need depicted on the charts consist of several elements as previously detailed, and thin solid lines map resources to specific needs, while light blue solid lines map resources to the entire needs category.

Finally, the future perspectives of these six genomics programmes – where publicly available – were reviewed to create a snapshot of how future plans respond to the needs identified, and giving some indication of where additional efforts might be concentrated. The results of this mapping are also shown the five figures below in blue boxes, with relevant recommendations from the Norwegian strategy for personalized medicine (denoted by a number and letter, e.g. A2) on the left of each figure and from other national genomics initiatives on the right.

1. Patient communication

Norwegian strategy for personalized medicine

Availability of genetic testing
Standardize clinical use of genetic testing and harmonize processes to ensure equal access to equal services (**B2**).

Patients identified through research
Analyze patient pathway that integrate clinic and research to establish uniform and harmonized combined patient pathways (**E2**).

Development of competencies and materials
Establish national network of regional competence centers for personalized medicine. Development of population targeted information and national competence standards for genetic counselling. (**A2, A3, A4, C4**)

Consent as part of a potential national solution
Development of quality requirements for and investigation of consent processes as part of a potential national solution for storage and processing of clinical genomic data (**B3, C4/D1**).

Existing tools and approaches

Clear selection criteria and referral processes
Selection criteria developed within flagship projects within cancer, rare disease (**AG, GE**) and infectious diseases (**GD, GE**). Specialist referals from hospitals for genetic testing (**AG, GD, GE**).

Standardized online educational resources for patients
Information and resources on genetic and genomic sequencing available online (**AG, GE, GD**).

Consent guided by genetic counsellor or equivalent
Disease-specific paper consent form (**GE**), 'CTRL' online dynamic consent management (**AG**). Guidance to facilitate and record self-determination over analysis, results and secondary and incidental findings (**AG, GD, GE**).

Standardized results
Return of findings through referring clinican/family doctor, with assistance of trained genomic medicine professional (**GE**). Return of negative findings by counsellor or referring clinician (**GE**).
Development of nationally standardized plain-language genomic test reports to improve accessibility to patients (**AG**).

Secondary findings
Opt-in for health-related secondary findings on consent form (**GD, GE**).

Continuous patient engagement
Feedback from any re-analysis performed through patients' doctor (**GE**). Research findings communicated to patient only if findings are actionable. Option for opting out or withdrawal of consent for participation in research projects (**AG, GD**).

Information to family members
Not by default but relatives can be referred to genetic testing, e.g. for rare diseases. Exception to necessity for consent in cases of disclosure required to lessen/prevent serious threat to health of patient or a genetic relative of the patient (**AG**).

AG, Australian Genomics, **GD**, Genomics Denmark, **GE**, Genomics England.

Needs

- Efficient identification and enrolment of eligible individuals
- Quality information on genetic testing
- Standardized dynamic consent management
- Return of results
- Active patient collaboration
- Ripple effects on family members

Examples from other national genomics initiatives

National genome projects or centres
National genome centres (DK, FI) or projects (EN, AU) enrolling rare disease, cancer and infectious disease patients.

Access to genetic testing
Equitable access to genetic testing (FI, SE), develop procedure for systematic evaluation and adoption of genetic tests (FI).

Genetic literacy education
Develop educational material targetting different groups including schools, general public, patients, and healthcare students and workers (EN, FI, SE).

Nationally aligned consent process
Development of nationally standardized consent process for clinical genomics (AU, EN), genome specific legislation (FI).

Target period for return of results
Results aimed to be returned to patients between 5-14 days (SE).

Patient engagement
Representatives from relevant patient organizations involved, also on management board (SE).

Benefits to family members
Harmonized national approaches to ensure results relevant to health of family members are released for their benefit (AU).

AU, Australia; DK, Denmark; EN, England; FI, Finland; SE, Sweden.

National and international guidelines, standards and recommendations

Access to availability of tests
Laboratories should publish online which genetic tests are offered for requisitioning clinicians to investigate (**VGU**).

Right to refuse testing
The individual's right not to be tested should be protected (**WMA**).

Information on genetic testing
Providing the patient with accurate and adequate information about genetic tests including purpose, nature, benefits, risks, burdens, limitations, return of and responding to results, additional findings, future discoveries, privacy, data security and data sharing (**WMA, ACMG1,2,3, VGU, GA4GH Consent Policy**).

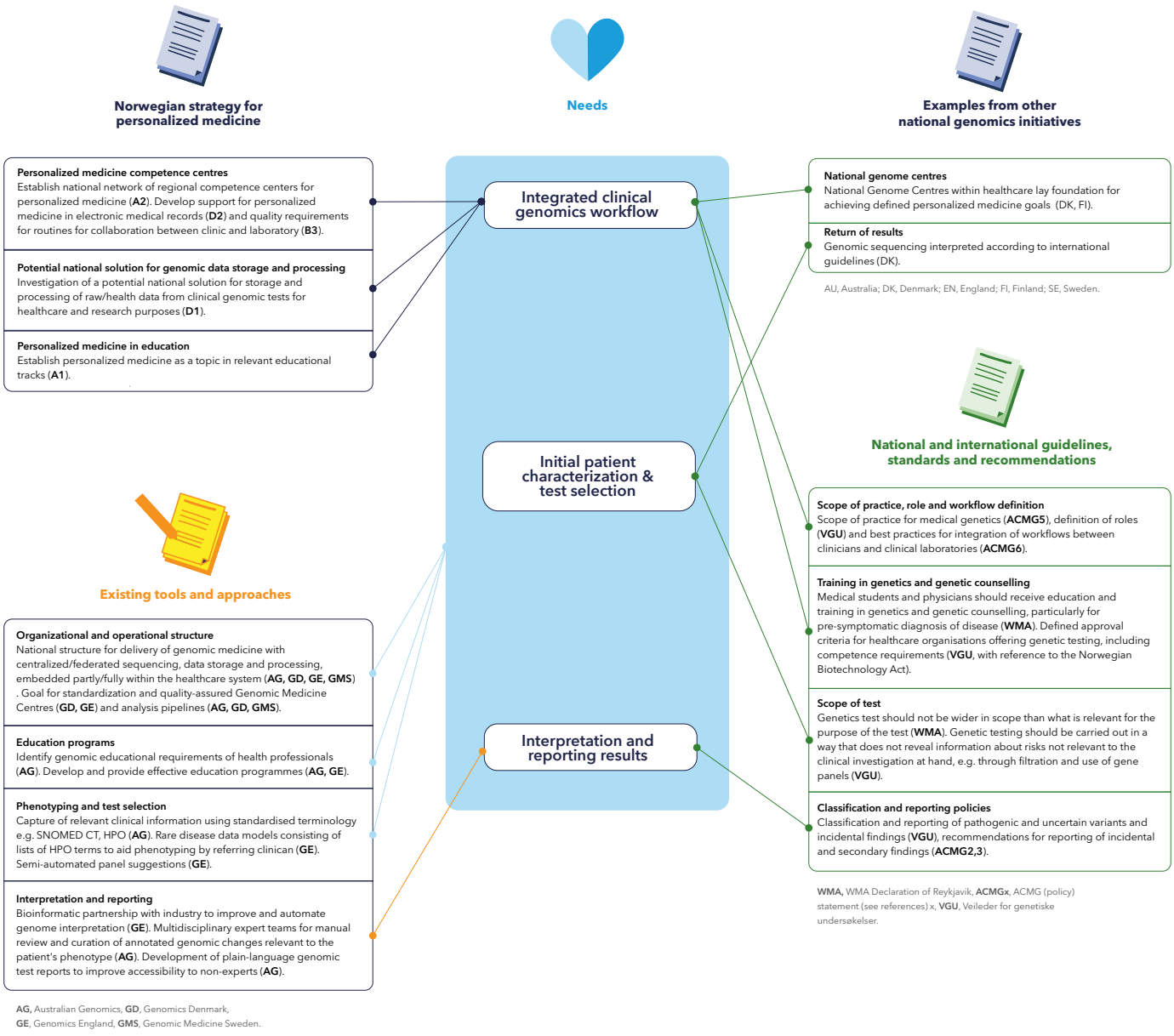
Informed consent as the basis for genetic testing
Genetic testing only to be done with informed consent of individual, for children only if in their best interests (**WMA, ACMG4**), with (written) consent gathered to address incidental findings, reanalysis and research purposes (**ACMG1, VGU**).

Genetic counselling for return of results
Appropriate genetic counselling should be offered for the interpretation of results, and enable the patient to make informed decisions, with no obligation for the individual to act on the results of the test (**WMA, VGU**).

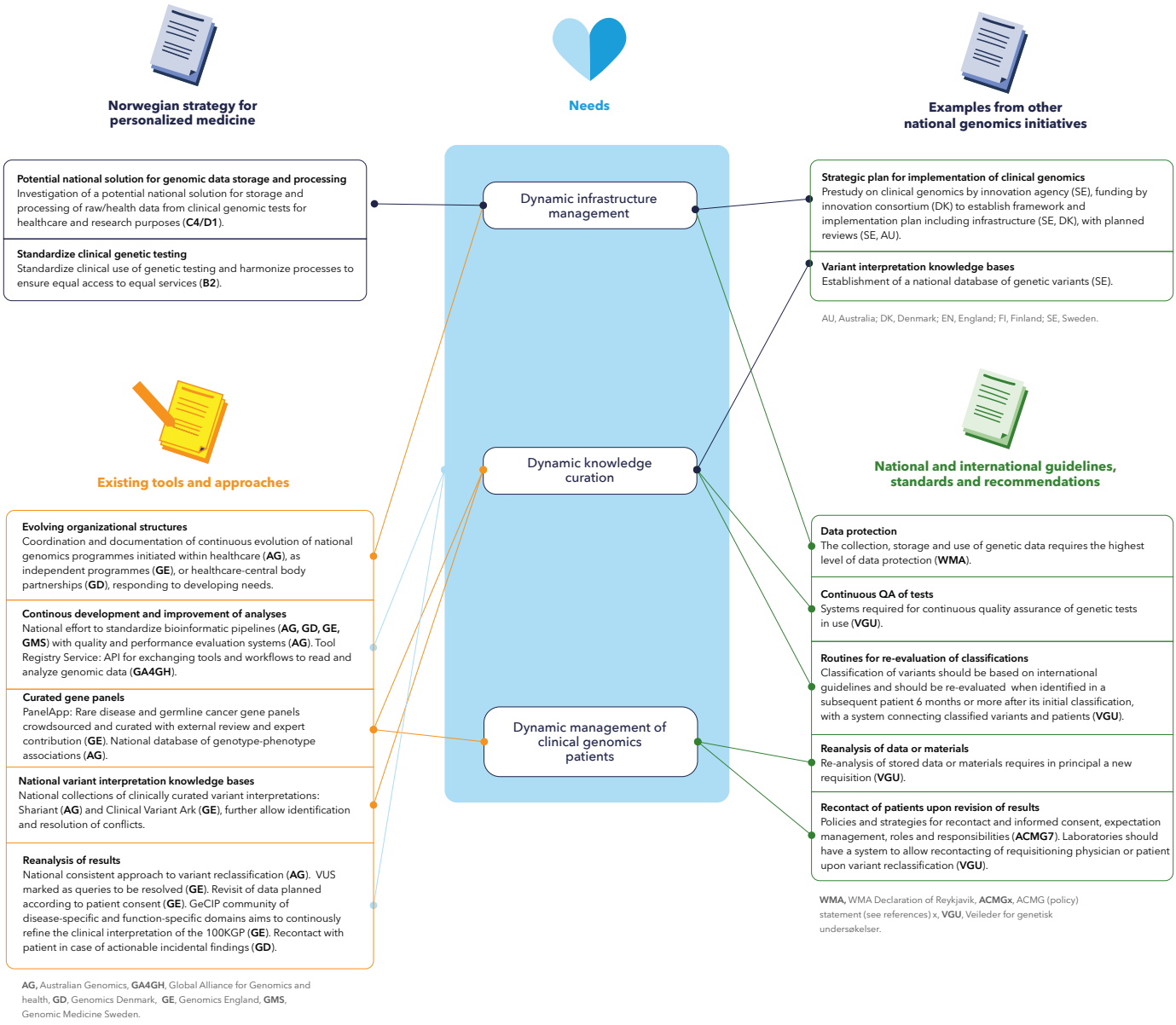
Strategy for third party implications
Test results with implication for close relatives should be discussed with patient with a focus on how to discuss the results with third parties (**WMA, VGU**). Regulations on providing information about potential risks to relatives without the patient's consent (**VGU,** with reference to the Norwegian Biotechnology Act).

WMA, WMA Declaration of Reykjavik, **ACMGx**, ACMG (policy) statement (see references) x, **VGU**, Veileder for genetiske undersøkelser.

2. Collaborative working models



3. Dynamic infrastructure, knowledge and patient management systems



4. Reciprocal knowledge and data sharing

Norwegian strategy for personalized medicine

Needs

Examples from other national genomics initiatives

Personalized medicine competence centres
Establish national network of regional competence centers for personalized medicine (**A2**).

Develop roles of relevant existing organizations
Potential of expanding the Cancer Registry to include information on cancer genetic variants (**C2**).

Holistic approach to clinical genomics
Analyze potential national solution for storage and processing of raw and analyzed genomic data and health data, including connecting with national/international health registers and solutions for associated healthcare and research, legal, ethical and technical issues (**C4/D1**).

For current and future patients

To build global knowledge bases

Data sharing for research

Secure cross-border data sharing

Clinical scope definition
Prioritise inheritable diseases and high-risk susceptibility (FI). Aim to provide access to genomic medicine for childhood cancer, complex diseases, hematology, infectious diseases, pharmacogenomics, rare diseases and solid tumours (SE).

Leveraging international genomics experience
Board of GMS with international experts from Denmark, Norway, Genomics England, Germany and Finland (SE).

Interface with (international) research
Genomic research must be international and deeply integrated in the healthcare system (DK), bringing together research, innovation, biobanks, industry partners (EN, FI, SE). Establishment of a national infrastructure to facilitate the use of genomic data in the development of new diagnostics, therapeutics and clinical studies (SE).

Multisite research ethics approvals
Streamline ethics approvals for multisite research studies and review governance frameworks for participation in large-scale international research efforts (AU).

AU, Australia; DK, Denmark; EN, England; FI, Finland; SE, Sweden.

Existing tools and approaches

Use of ontologies and standards
Including HPO, SNOMED CT, FHIR, HGVS (**AG, GE**). Phenopackets for exchanging genotypic and phenotypic information (**GA4GH**). Htsget and refget: genomic data retrieval specifications for target or reference dataset (**GA4GH**).

National reference data sets
Creation and publication of Swegen (Sweden), Danish Reference Genome, FinnGen (Finland, genotyping).

Data sharing services
ClinVar, Beacon, Matchmaker Exchange to query for genetic variant and/or phenotypic information.

Permissions, privacy and security
Access to and processing of data implemented as determined by consent, governance, ethics committees, data protection agencies and GDPR (**AG, GD, GE**). Consent codes support recording of data use categories and requirements (**GA4GH**). Consent tools: International data sharing prospective consent form and clauses for local adaptation (**GA4GH**). DUO: data use ontology that allows users to semantically tag genomic datastes with usage restrictions and making them automatically discoverable based on authorization level (**GA4GH**). Anonymous, coded, deidentified data used to safeguard privacy (**AG, GD, GE**). Crypt4GH file format allows storage of encrypted and authenticated data (**GA4GH**). Data breach testing (**AG**).

Collaboration with academia
Data available for national and international research by applying, tiered access (encrypted, **AG**; through GeCIP, **GE**). Health Data Research Alliance unites expertise to establish best practice in the stewardship of the UK's health data (**GE**).

Collaboration with industry
Forums and working models to allow partnership between national genomics initatives and small, medium and large industry (**AG, GD, GE, GMS**) aiming to maximize patient benefit (**GE**), and access to data by private entities if consented to (**AG**). Catapaults to accelerate medicines and therapy discovery through multi-stakeholder engagement (**GE**).

AG, Australian Genomics, **GA4GH**, Global Alliance for Genomics and health, **GD**, Genomics Denmark, **GE**, Genomics England, **GMS**, Genomic Medicine Sweden.

National and international guidelines, standards and recommendations

Duty to share data
Responsible sharing of genomic variant and phenotype data provides the information necessary to improve clinical care, and empower device and drug manufacturers that are developing tests and treatments for patients (**ACMG8**).

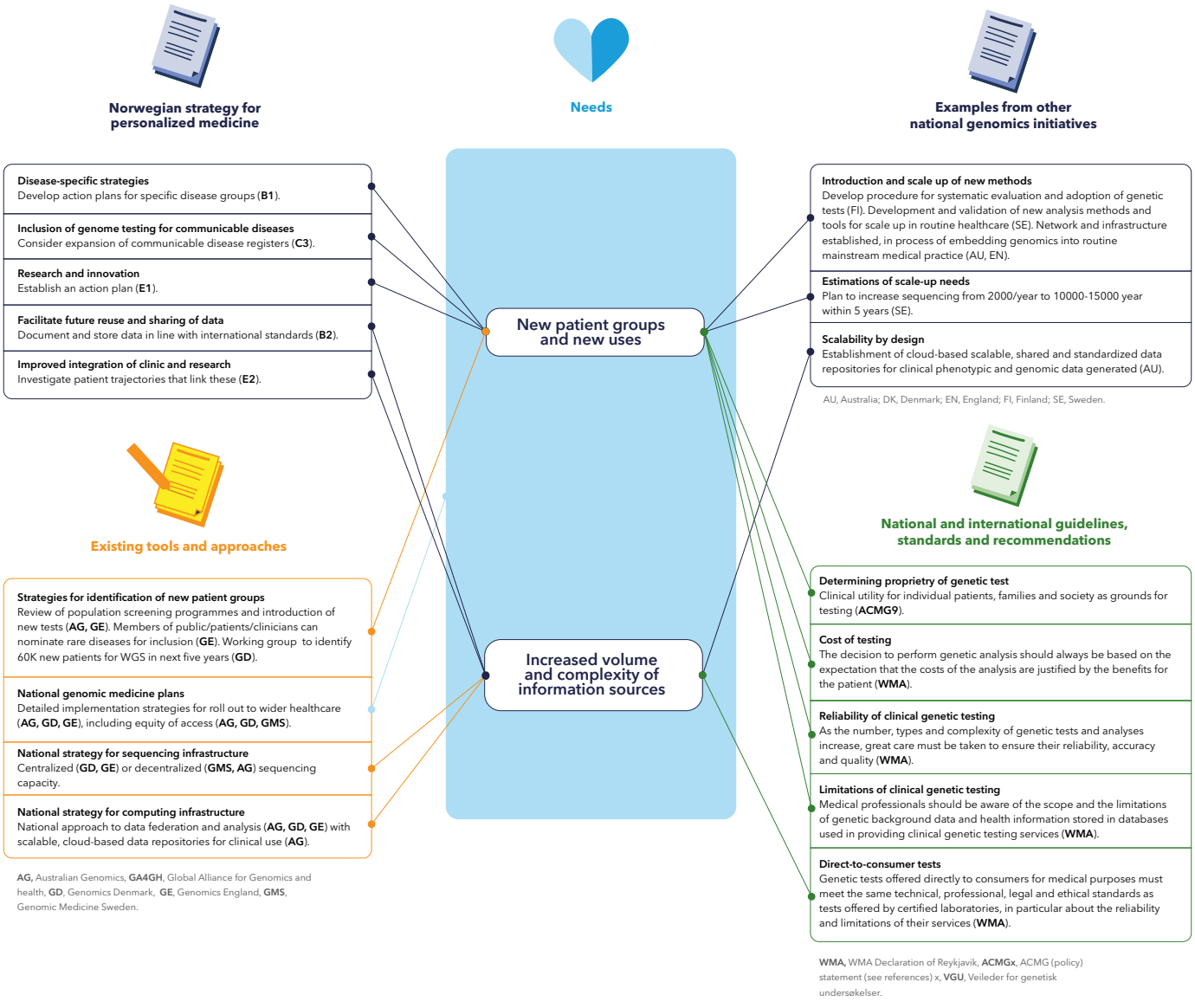
Actionable findings from research participation
Research participants must be informed of the possibility of findings indicating serious health threats when relevant, and be referred to genetic counseling and medical intervention in such an event (**WMA**). Even if the scope of research is related to the condition of a patient who has contributed data, these results are not necessarily returned to the patient (**VGU**, with reference to Norwegian National Research Ethics Committees).

Use of FAIR principles
FAIR principles for scientific data management and stewardship: Findable, Accessible, Interoperable, Reusable (**WMA**).

Privacy, security and accountability in data sharing
GA4GH Privacy and Security Policy guides secure sharing of genomic and health data. **GA4GH Data Security Infrastructure Policy** describes security infrastructure policy and technology recommended for international genomic data sharing. **GA4GH Accountability Policy** guides transparent and accountable data sharing, and monitoring and responding to non-compliance with data sharing standards.

WMA, WMA Declaration of Reykjavik, **ACMGx**, ACMG (policy) statement (see references) x, **VGU**, Veileder for genetisk undersøkelser.

5. Future challenges



CONCLUDING REMARKS

While the use of clinical genomics is clearly established for particular indications, such as the diagnosis of rare disease, hereditary cancer and guiding cancer treatment, the discipline continues to face challenges resulting from its relatively recent transition from research into the clinic, as well as continued research that uncovers new uses and scopes for this technology. The paradigm shift of personalized medicine in general and clinical genomics in particular means its wide-scale implementation faces many barriers as described in the BigMed report of 2018 [13], specifically related to legal and regulatory, organizational, financial and political, technical, and competence and knowledge.

Many countries have recognized both the promise and challenges of rolling out clinical genomics at scale to their citizens, and have accordingly published and implemented strategies and projects to catalyse the transition to clinical production of genomes, organized within existing healthcare organizations, or through the creation of umbrella organizations such as in Genomics Denmark, or completely externally as change agents, such as Genomics England. In the process different approaches are being explored globally, including centralized versus distributed resources for sequencing, data storage and computing in the cloud or on-premise, clinical interpretation and return of results infrastructure and services. The decisions to be taken on these issues will additionally need to balance cost, national and global standardization considerations, but will gain robustness and continued relevance by addressing and responding specifically to the needs described in this white paper.

Genomics challenges the traditional division of healthcare and research, and raises the vital question about the extent to which data from these two domains should be made reciprocally available. Multidisciplinary and public education, engagement and debate on the risks and opportunities associated with genomic medicine are all crucial groundwork for defining the breadth of wider use of data and for which purposes, and collectively setting priorities for this work.

Finally, it will be necessary to consider the needs identified in wider contexts of both the healthcare unit or system in which it is embedded, and concrete international activities relevant for clinical genomics. More clinical areas such as pathology and microbiology are also experiencing a move towards treatment tailoring and personalization of clinical decisions, with the accompanying needs of higher data storage and processing capacity, and complex clinical decision support. Aligning needs with other medical disciplines moving from innovation to clinical production may have positive synergistic effects.

As of January 2020, Norway and 20 European Union member states have signed the declaration 'Towards access to at least 1 million sequenced genomes in the EU by 2022' [14]. This initiative to link genomic data across the EU clearly underlines the need to explore and develop federated models that enable cross-border clinical genomics data sharing that leverage on both existing and new repositories, with the ultimate aim of providing cross-border, data-driven healthcare to its citizens.

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NATIONAL GENOMICS STRATEGIES AND INITIATIVES

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GUIDELINES, STANDARDS AND RECOMMENDATIONS

WMA
Declaration of Reykjavik – ethical considerations
regarding the use of genetics in healthcare

ACMG1
ACMG Policy Statement: Points to consider for informed consent for genome/exome sequencing https://www.acmg.net/PDFLibrary/Informed-Consent-Genome-Exome-Sequencing.pdf

ACMG2
ACMG Statement: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0) https://www.acmg.net/PDFLibrary/Reporting-Secondary-Findings.pdf

ACMG3
ACMG Policy Statement: Recommendations for reporting of incidental findings in clinical exome and genome sequencing https://www.acmg.net/PDFLibrary/Reporting-Incidental-Findings.pdf

ACMG4
ACMG Policy Statement: Technical report: ethical and policy issues in genetic testing and screening of children https://www.acmg.net/PDFLibrary/Ethical-Policy-Issues-Genetic-Screening-Children.pdf

ACMG5
ACMG Policy Statement: Scope of practice: a statement of the ACMG https://www.acmg.net/PDFLibrary/Scope-Of-Practice.pdf

ACMG6
ACMG Statement Professional responsibilities regarding the provision, publication, and dissemination of patient phenotypes in the context of clinical genetic and genomic testing: points to consider. https://www.acmg.net/PDFLibrary/Patient-Phenotypes-Professional-Responsibilities.pdf

ACMG7
ACMG Policy statement: Patient re-contact after revision of genomic test results: points to consider. https://www.acmg.net/PDFLibrary/Patient%20recontact.pdf

ACMG8
ACMG Statement: Laboratory and clinical genomic data sharing is crucial to improving genetic health care. https://www.acmg.net/PDFLibrary/Genomic-Data-Sharing-Policy-Statement.pdf

ACMG9
ACMG Policy Statement Clinical utility of genetic and genomic services. https://www.acmg.net/PDFLibrary/Clinical-Utility-Genetic-Genomic-Services.pdf

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Ullevål sykehus

SAFER, SMARTER, GREENER

DNV GL AS
NO-1322 Høvik, Norway
Tel: +47 67 57 99 00
www.dnvgl.com

Sharmini Alagaratnam
Principal researcher
Precision Medicine Program
DNV GL Group Technology
and Research (GTR)

E-mail: sharmini.alagaratnam@
dnvgl.com
Mobile +47 9937 1772

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