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Lessons learnt from national implementation of whole genome sequencing

RARE HEREDITARY DISEASES

Consolidated Report 2024

Contents

Preface

Based on the Danish national strategy for personalised medicine and the grant from the Novo Nordisk Foundation, the Danish National Genome Center (NGC), in collaboration with the Danish regions and clinical environments, has successfully implemented a systematic whole genome sequencing programme for 17 patient groups in Denmark, selected based on medical criteria. We have jointly implemented an advanced technology in the national healthcare system with a direct clinical application that creates value by means of improved diagnostics, improved patient care and the possibility of more targeted treatment for the individual patient and their family. A programme that will benefit many patients in the long run and that we in Denmark can be proud of.

The clinical environments indicate in their feedback on the implementation that the initiative provides clear clinical effects.
The Danish whole genome sequencing programme offered to patients in need of genetic diagnostics follows the technological advancements in the field and is fully in line with programmes offered abroad.

The national implementation of whole genome sequencing has also contributed to increased health equality, competence building and a new national structure, as well as strengthened interdisciplinary collaboration at all levels for the benefit of the patients.

We also note a strong desire for continued systematic patient involvement and continued national coordination with a uniform programme for all patients. In addition, there is emphasis on the need for monitoring efficacy through consolidation with clinical data.
The lessons learnt from this implementation clearly show that when we collaborate across national, regional and health professional competencies and specialties, we can realise ambitious strategies to develop the Danish healthcare system for the benefit of the patients.

The programme offered to the 17 patient groups has enabled the creation of a common national infrastructure for comprehensive genetic diagnostics, including the establishment of the National Genome Database, which today contributes to patient care in the healthcare system. On 1 May 2024, NGC opened up access to the genome database for researchers with research ethics approval so that even more future patients can benefit from the technological advances that are constantly developing and continuously create new opportunities for patients in Denmark.

Thank you to everyone who has contributed!

Bettina Lundgren
CEO

Summery

Based on the Danish national strategy for personalised medicine, 17 patient groups (13 patient groups with rare hereditary diseases and four patient groups with cancer) have been given access to whole genome sequencing as part of their diagnostic assessment and treatment. The programme has been implemented nationally on the basis of guiding principles of health equality, professional assessment and value for the patient and kick-started by a grant from the Novo Nordisk Foundation. The patient groups have been nominated by clinicians nationally and selected after a thorough medical review process to include patients who are believed to have a genetic cause for their disease and are therefore reckoned to benefit from the programme in terms of better diagnosis and treatment. At the same time, the programme is limited to patient groups/disease areas where, prior to implementation, there was (some) experience with the clinical use of (comprehensive) genetic diagnostics to ensure that the clinical potential is realised in the best possible way.

The experiences from each patient group have been compiled in a status report that evaluates the implementation and elucidates the effect of whole genome sequencing for the patient group in a uniform way that allows cross-comparison (Professional recommendations (ngc.dk)). The effect of whole genome sequencing is analysed from four perspectives with national experiences illustrated through patient cases and interviews with clinicians, and international perspectives illustrated through reviews of literature and programmes in comparable countries.

This report compiles the Danish National Genome Center's overall lessons learnt from the implementation of whole genome sequencing across the **thirteen patient groups with rare hereditary** diseases. For these groups, **a total of 16,870 samples have been sequenced** since the inception in 2021, with a process time of 17 days. The lessons from the four patient groups with cancer are described separately, although there may be overlaps between the 17 patient groups.

National experiences, illustrated by patient cases and interviews with clinicians, show that across the 13 patient groups with rare hereditary diseases, the programme is of great importance to **patients and clinicians in terms of better patient pathways and better diagnostics and treatment**. In addition, there is the issue of **clarification of heredity**, where the diagnosis of patients with hereditary disease has consequences that can extend into the family, with implications for follow-up and treatment in relatives. The use of whole genome sequencing in the selected patient groups is considered to be clinically relevant as the patients **benefit specifically from the programme** in terms of better diagnostics and the possibility of targeted follow-up/treatment. Both clinicians and patient organisations consequently want the use of whole genome sequencing to continue, as it provides **important technological advantages and is a natural step in the development in the field. For some patient groups**, there has been a need for minor adjustments along the way based on experience from the implementation or new knowledge in the field, which must also be expected in the future due to the rapid technological and knowledge advancements in the field. However, the implementation has also been a **comprehensive process** requiring significant reorganisation of regional work processes in the laboratory and clinic. The lessons learnt described in this report show an **immediate effect** of whole genome sequencing, but overall it is estimated that the full effect of the implementation has not yet been realised. **The effect will further materialise over time**, partly due to the possibility of reanalysis of data, the ability to apply the latest knowledge to examinations and in line with technological and knowledge developments.

Follow-up research is ongoing at local/regional level, with the aim of elucidating the effect of implementing whole genome sequencing in specific patient groups, but the results have not yet been analysed.

Across the patient groups, it is emphasised that the uniform and systematic programme has contributed greatly to **equality in health** and a common platform for collaboration. The national implementation has significantly **strengthened interdisciplinary collaboration at national level** and has contributed to **competence building** broadly in terms of knowledge and use of advanced genomic diagnostics. Overall, the insights gained show that the national implementation has **achieved significant strategic goals of increased collaboration and knowledge sharing for the benefit of the patients.**

The overarching national experience shows that the national strategy for personalised medicine and the grant from the Novo Nordisk Foundation have helped facilitate the implementation of a **new advanced technology in the healthcare system in the form of whole genome sequencing offered to nationally consolidated patient groups based on medical criteria**. Furthermore, a national infrastructure has been built for analysis and secure sharing of data. It can also be seen that it is possible to realise visionary strategies for the development of the Danish healthcare system for the benefit of the patients when **collaborating nationally, regionally and across healthcare competencies and specialties.**

The international perspectives, illustrated by systematic literature reviews for the 13 patient groups, show that access to **comprehensive genetic diagnostics is crucial to ensure diagnostic clarification for patients** with rare hereditary diseases. An accurate diagnosis is essential for ensuring individualised or targeted treatment and follow-up for patients with rare diseases. For example, **a recent large meta-analysis found a clinical effect in 61-77% of patients with rare diseases** where a genetic diagnosis made by whole genome sequencing led to changes in the clinical management of patients. In addition, an accurate diagnosis enables family assessments and ensures that (only) relevant risk persons in the family are offered follow-up. The central importance of genetic diagnostics is underlined by international clinical recommendations in this area. The **technological superiority of whole genome sequencing** also means that **more patients receive an accurate diagnosis compared to standard genetic testing**, and the diagnostic yield has increased over time due to advances in knowledge and technology. At the same time, clinical effect is reported to increase over time, which is expected to accelerate further as targeted treatment options improve. Another important point is that **the effect of whole genome sequencing described for the Danish patients/patient groups aligns with international experiences** and that the programme offered to the 13 Danish patient groups is consistent with programmes in comparable countries, indicating that **Denmark with the programme is in line with international developments. Also, the applications of whole genome sequencing are expected to expand along with technological and knowledge developments and the important transition to more personalised medicine.**

The international perspectives/experiences support the existence of **well-documented clinical effects of (comprehensive) genetic diagnostics** for patients with rare hereditary diseases, as also reflected in international clinical guidelines and disease classifications. The **use of whole genome sequencing is well documented in a number of disease areas** that overlap with the Danish patient groups.

Finally, it should be noted that this consolidated report highlights experiences with the national implementation of whole genome sequencing, while health-economic aspects of the Danish initiative have been analysed elsewhere and are therefore not part of this report. In Denmark, there has been no tradition of assessing the clinical effect or health economic implications of genetic diagnostics at national level, but **internationally, there is substantial experience with the clinical use of whole genome sequencing for disease areas that overlap with the Danish patient groups with rare hereditary diseases**. In addition to clinical effect, these experiences also assess technical and health economic perspectives. For example, a number of studies point to a **higher diagnostic yield and/or shorter time to diagnosis when using whole genome sequencing** compared to standard genetic testing in people with developmental disorders or rare suspected genetic diseases or congenital anomalies. Furthermore, there is emerging evidence that using **whole genome sequencing as the first choice may be cost-effective in children with developmental disorders** or suspected genetic disease, compared to standard genetic testing. As the clinical effect in Danish patients is similar to that described in international patients, technical and health economic insights gained internationally may be assumed to be relevant for Denmark, but a specific assessment of this will require systematic compilation of clinical data.

Purpose and basis of the report

The Danish Government and Danish Regions agree that the Danish strategy for personalised medicine in the healthcare system should focus on point-of-care and clinical needs. Part of realising this goal is the development of personalised medicine by extending whole genome sequencing to a number of patient groups and rare diseases in order to understand the diseases based on the patients' genome, thereby providing improved diagnostics and treatment. As part of the strategy, the Danish National Genome Center (NGC) has been established to build a secure national infrastructure for clinical use and research. In order to kick-start the development, a grant from the Novo Nordisk Foundation has allocated funds to conduct up to 60,000 whole genome sequences in the healthcare system. From 2024 onwards, funding has been earmarked in the Finance Act for a new strategy for personalised medicine, including for the infrastructure for developing personalised medicine and the governance structure for NGC. The latter aims to ensure consolidation, coordination and a common national direction for national implementation of whole genome sequencing.

A guiding principle in the implementation of the national strategy for personal medicine is equality in health. All patient groups offered whole genome sequencing via the NGC infrastructure must be consolidated nationwide so that the programme for all patients is the same, no matter where in the country they are diagnosed. A guiding principle is that patients should have rapid access to the improvements made possible by whole genome sequencing. Access to fast and better treatment nationally can be made possible by facilitating national knowledge sharing and dissemination of the experiences and competencies of the strong clinical and research environments that already have experience in realising the clinical potential of comprehensive genetic analyses, including whole genome sequencing in diagnostics and patient treatment. This means that in addition to the specific access to whole genome sequencing, it is also an important success parameter in the implementation of the national strategy for personalised medicine that the implementation phase supports increased national collaboration and knowledge sharing.

This consolidated report aims to provide an overview of the lessons learnt from the national implementation of whole genome sequencing for the 13 patient groups that include rare hereditary diseases, who are currently being offered whole genome sequencing as part of their treatment. A similar consolidated report has been prepared for the four cancer patient groups.

Patient groups

A total of 17 patient groups are currently being offered whole genome sequencing via the national infrastructure as part of their treatment in the Danish healthcare system. Nominated by clinicians all over the country or by medical societies, the patient groups have been selected through an extensive medical review process, focusing on professional assessment and value for the patient and access to faster and better treatment nationally, which are two of the guiding principles of the strategy for personalised medicine.

The patient groups can be divided into patients with rare hereditary diseases (13 patient groups) and patients with cancer (4 patient groups), although there may be overlaps between the 17 patient groups. The 17 patient groups comprise about 90 disease areas that are all suspected to have a genetic cause. Genetic diagnostics therefore plays an important role in the diagnosis and thus in identifying treatment options for these diseases.

This report will consequently follow up on the effect of implementing whole genome sequencing for the following 13 patient groups with rare hereditary diseases, including the organ-specific rare diseases:

1. Inherited cardiac disease
2. Hereditary haematological disease
3. Hereditary cholestatic and fibrotic liver diseases
4. Audiogenetics
5. Endocrinological patients
6. Foetal medicine
7. Neurogenetic patients
8. Kidney failure
9. Ophthalmology
10. Primary immunodeficiency
11. Psychiatry, children and adolescents
12. Rare diseases in children and adults
13. Severe hereditary skin diseases

National specialist networks: Realising the clinical potential for patient access to whole genome sequencing

For each included patient group, a national specialist network has been established consisting of:

- Clinicians with experience in comprehensive genetic testing for the patient group, appointed by the regions and the Organization of Danish Medical Societies
- A patient representative appointed by Danish Patients
- A representative appointed by the regions' clinical quality development programme

Danish Patients and the regions' clinical quality development programme have not appointed representatives to all specialist networks.

The purpose of the national specialist networks has been to contribute to the best possible realisation of the clinical potential for access to whole genome sequencing for the patient group. The specialist networks have aimed to ensure that patients across the country have equal access to whole genome sequencing through coordinated and uniform deployment and clinical use of the national infrastructure. In this context, >140 meetings have been held with the participation of >150 specialists and patient representatives to prepare recommendations and status reports for the patient groups.

Status reports

Status reports have been prepared for all 17 patient groups, including both patients with rare hereditary diseases and with cancer. The method description can be found at www.ngc.dk. The status reports describe the lessons learnt from the national implementation of whole genome sequencing for the patient group and have been approved by the specialist networks. The status reports follow a model that ensures uniform assessment of the patient groups while allowing for cross-comparison. The method description can be found at www.ngc.dk.
The parameters included in the status reports and in this consolidated report have been decided by the steering committee for the implementation of personalised medicine and contain the following:

Implementation status for whole genome sequencing

- Number of whole genome sequences requested per region/patient group.
- Process time (time from sample receipt to release of data for interpretation).

Illustration of the effect of whole genome sequencing through four perspectives

- Patient cases to illustrate the added value of whole genome sequencing compared to other genetic analyses.
- Semi-structured interviews with clinicians and (for some patient groups) patient representatives to elucidate experiences with the national implementation of whole genome sequencing.
- Systematic literature reviews to illustrate the clinical effect of using comprehensive genetic diagnostics for the patient group.
- Comparison of the use of whole genome sequencing internationally (England, France and Sweden).

The lessons learnt from the status reports for the 17 patient groups are further supplemented with

- Interviews with patient representatives to further elucidate the patient perspective on the implementation of whole genome sequencing.
- Interviews with members of the working group on clinical applications of whole genome sequencing to clarify whether/how the guiding principles of professional assessment and value for the patient and access to faster and better treatment have been met.

This report contains the Danish National Genome Center's compilation of overall lessons learnt from the status reports for the 13 patient groups with rare hereditary diseases, supplemented with perspectives obtained from interviews with patient representatives and the working group on clinical applications of whole genome sequencing.

Health economic analysis is not part of this report. Under the auspices of the steering committee for the implementation of personalised medicine, a working group has been set up to evaluate the operational and health economics of providing whole genome sequencing. Clinical patient data to illustrate the effect are not included in the status reports or in this consolidated report, as data currently must be collected manually. Based on a pilot test, it was assessed that the benefits were not commensurate with the effort. It is expected that, over time, the lessons gathered in the status reports and the consolidated reports for the patient groups will be supported by clinical quality data and follow-up research.

National implementation of whole genome sequencing in the 13 patient groups

Overall, the implementation shows wide variation in terms of experiences with the use of whole genome sequencing, both between patient groups and within/across regions. This is reflected in the status reports for the individual patient groups. Some patient groups have been using whole genome sequencing (for selected indications) in parts of Denmark for a long time prior to start-up, and the programme has now been implemented nationally. For other patient groups, the use of targeted genetic diagnostics has been established within highly specialised functions, while the use of comprehensive genetic diagnostics such as whole genome sequencing is a new technology which, thanks to the national initiative, is well on its way to becoming a systematic part of diagnostic pathways for many patient groups.

Despite the different starting points, there are overlapping experiences from the national implementation of whole genome sequencing in the 13 patient groups. The common denominator is that the programme has been consolidated nationally for the benefit of the patients, although the implementation process has been extensive.

Number of whole genome sequences per region/patient group

The implementation status is illustrated by the number of whole genome sequences requested per patient group. The number of "samples" or "analyses" refers to the number of whole genome sequences with a sequencing depth of 30X (referred to as a genome equivalent). In patients with rare hereditary diseases, one sample generally corresponds to one genome equivalent. Ordering whole genome sequencing can sometimes trigger multiple samples/analyses, for example when conducting family testing (trio-analysis of child + parents), which totals three samples. The need for trio-analyses has been described in several patient groups, but NGC is not able to calculate the proportion of trio-analyses out of the total number of samples sequenced. This means that the total number of samples for the patient groups is not necessarily the same as the number of patients.

The national specialist networks for the 13 patient groups with rare hereditary diseases have reported an annual requirement of 15,907 samples for newly referred patients. Since the first pilot group started in 2021, 16,870 samples have been sequenced for the 13 patient groups.

In April 2022, the Danish National Genome Center (NGC) announced that it would be ready to receive samples from all patient groups. The different patient groups were reported ready to the region between July 2022 and September 2023, after which the programme has been implemented for all patient groups at national level.
After an implementation period in 2022, the number of samples for the 13 patient groups is relatively stable at approximately 800 samples per month, corresponding to approximately 10,000 per year (Figure 1). However, a slight increase in the number can be observed over the last six months. From 1 November 2023 to 1 May 2024, the total sequencing has corresponded to 67% of the reported number of samples for newly referred patients.

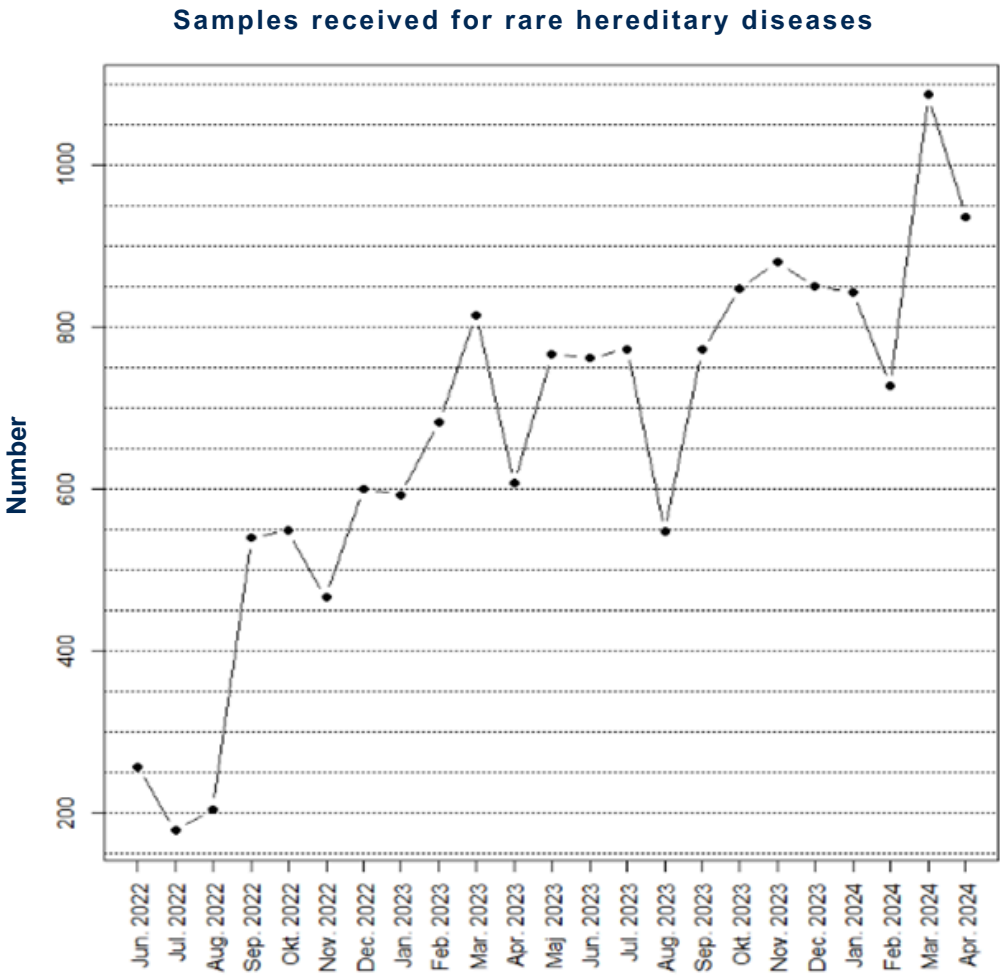

Figure 1 shows the development in the number of samples sequenced for the 13 rare hereditary disease patient groups.

Table 1 shows the number of samples submitted for each of the 13 patient groups and the percentage of samples submitted relative to the reported number from November 2023 to May 2024. There is a significant variation in the percentage of samples submitted within the patient groups, from 26% to 135%.

Patient group	Equivalents total	Percentage submitted for newly referred patients November 2023 to May 2024
Inherited cardiac disease	1421	84%
Hereditary haematological disease	602	135%
Hereditary cholestatic and fibrotic liver diseases	121	49%
Audiogenetics	589	56%
Endocrinological patients	569	105%
Foetal medicine	819	51%
Neurogenetic patients	1771	74%
Kidney failure	276	93%
Ophthalmology	372	59%
Primary immunodeficiency	1013	87%
Psychiatry, children and adolescents	367	26%
Rare diseases in children and adults	8668	69%
Severe hereditary skin diseases	282	49%
Total	16870	67%

Table 1 Total number of samples submitted and the percentage of the expected number for newly referred patients between 1 November 2023 and 1 May 2024.


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Process time

The process time (time from sample receipt until data is released for interpretation) is calculated monthly and can be found on ngc.dk. The process time for March 2024 was 17 days. The process time was slightly longer during start-up (e.g. 21 days in September 2022), but has since remained stable despite increasing sample numbers, cf. Figure 2. Due to the need to analyse many samples in parallel on the sequencing machines, **an increased sample number can potentially lead to a lower process time.**

The provision of whole genome sequencing to the patient groups is delineated based on process time, which means that certain acute indications are analysed outside the national infrastructure due to the need for an urgent response in the interest of patient treatment. These analyses are consequently not covered by the implementation data in this report or in the status reports, although the specialist networks point out that some of these patients could benefit from access to whole genome sequencing.

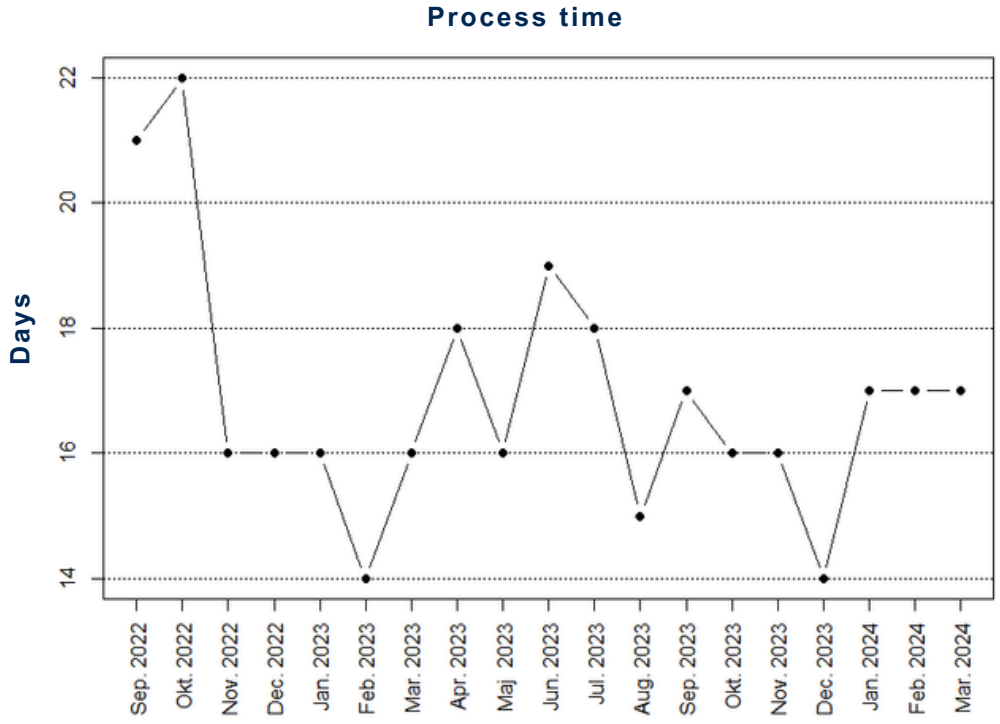

Figure 2 shows the monthly process time for 90% of all samples for the 17 patient groups in the period September 2022 to March 2024.

Lessons learnt by specialist networks from the implementation of whole genome sequencing

The specialist networks report that the implementation of systematic provision of whole genome sequencing as part of diagnosis and treatment for 13 patient groups has been **a major task, and it has taken time to adjust the relevant workflows** involving both the organisation in the laboratory and the clinical work processes. It has also taken time to disseminate knowledge about the programme and the ordering process in the clinical environments, as well as to systematise the use of genetic studies for some of the patient groups. This explains the gradual implementation of the whole genome sequencing programme shown in Figure 1, which is not yet expected to be fully implemented for some of the patient groups. Overall, the specialist networks believe that while the full effect of the implementation has not yet been realised, it is expected to materialise over time.

Based on the feedback from the specialist networks, we do not expect to reach 100% of the reported number of samples for most patient groups. This is because there is **a natural overlap between several patient groups, meaning that samples can be submitted under multiple indications**. At the same time, some specialist networks believe that the **expected sample size was set too high initially**. Finally, some specialist networks report that patients have not come in at the expected pace, and that some **patients decline the test**, just as some clinicians may be reluctant to provide the analysis for financial reasons and possible concerns about overdiagnosis. In addition, due to the large number of samples, **resources for interpretation have turned out to be insufficient, resulting in prolonged response times**. For some specialist networks, this has led to a practice where you may **start with less comprehensive genetic analyses, resulting in fewer samples subsequently sent for whole genome sequencing**.

The specialist networks also report that the implementation of the national whole genome sequencing programme for the 13 patient groups **represents a significant and important technological advancement that should continue** due to its major importance for patients and clinicians alike, as illustrated in the following section.

> “the implementation of the national whole genome sequencing programme represents a significant and important technological advancement which should continue”

Illustration of the effect of whole genome sequencing through four perspectives

National experiences illustrated by patient cases and interviews with clinicians show that:

- **Whole genome sequencing offers technological advantages with the potential for faster and more accurate diagnostics, improving pathways and treatments of patients with rare hereditary diseases.** This provides clarity for patients and their families and can potentially improve quality of life. The selected patient groups are **clinically relevant and the use is in line with international practice.**

- Implementing whole genome sequencing nationally has greatly **strengthened national and international collaboration** and improved research opportunities. The programme has contributed to **increased knowledge sharing and competence development as well as to equal access for patients nationally.**

- Implementation challenges include a **lack of interpreters, as well as logistical challenges** relating to requisition and consent, and require continued investment and commitment to realise the full potential.

International perspectives illustrated by literature review and experiences from comparable countries show that:

- Comprehensive genetic diagnostics such as **whole genome sequencing play a key role in ensuring diagnostic clarification in patients with rare hereditary diseases**, reducing unnecessary examinations and contributing to better treatment pathways for patients and their families.

- **Diagnostic yields and clinical effect are increasing over time** and are expected to increase further as knowledge and technology advances and targeted treatment options improve.

- With the programme, the use of whole genome sequencing in **Denmark is in line with available programmes** in comparable countries, indicating that Denmark is in line with the development internationally.

The four perspectives include both the technological advantages of whole genome sequencing and the clinical effect of being diagnosed. In summary, experience shows that comprehensive genetic diagnostics through whole genome sequencing plays a key role for patients with rare hereditary diseases and **the use and benefits are expected to increase in the future**. Furthermore, the clinical effect of whole genome sequencing described for the Danish patients/patient groups is **consistent with the clinical effect described in the literature and the use in comparable countries, which supports that international experiences can help elucidate the use of whole genome sequencing in Danish patients.**

National experiences from patient cases

In connection with the preparation of the status reports for the patient group, the specialist networks have submitted a total of 39 patient cases to illustrate the added value of whole genome sequencing compared to other genetic tests. Focus has been on the implications for the patient and their family, as well as potential derived effects of implementing whole genome sequencing, e.g. a uniform programme across Denmark, increased focus on the patient group, interdisciplinary and/or national collaboration, etc.

The following is a summary of key lessons learnt from the submitted patient cases:

- Whole genome sequencing can help **speed up diagnostic clarification**, shortening an often lengthy diagnostic process that can be both frustrating and stressful for patients.

- **Whole genome sequencing offers a technological advantage** compared to other genetic analyses, resulting in improved detection of structural variants and variants outside the coding regions. Whole genome sequencing enables an increased number of diagnoses, which improves patient care and treatment and potentially helps prevent ineffective treatments or unnecessary interventions.

- A genetic diagnosis contributes to diagnostic clarity, which can be crucial in **understanding and managing the disease**, and also removes the uncertainty through diagnostic clarification.

- A genetic diagnosis provides a **more accurate prognosis, which is crucial for implementing targeted treatment strategies** and individual control programmes and treatment choices that are better adapted to the patient's needs and the characteristics of the disease.

- A genetic diagnosis also provides clarity about **recurrence risk and enables reproductive choices** such as prenatal genetic testing and Preimplantation Genetic Testing (PGT), which affects the family's future planning and decisions, for example, about additions to the family.

- A genetic diagnosis also allows for **genetic testing of family members,** including clearance of relatives and identification of relatives at risk who need follow-up/treatment. Early diagnosis allows for early intervention that can potentially delay or prevent disease progression.

- A genetic diagnosis can also provide access to **research projects with new treatments** and contribute new knowledge in the field.

National experiences from interviews with clinicians

Between March 2023 and January 2024, a total of 13 semi-structured interviews were held with all specialist networks and additional people invited from among the regions' contact persons for personalised medicine. The purpose was to gather significant experiences from point-of-care staff for a qualitative assessment of the clinical effect of implementing whole genome sequencing. There has also been a focus on possible other derived effects of implementing whole genome sequencing, e.g. in the form of uniform programmes nationally, increased medical focus on the patient group, interdisciplinary and/or national collaboration.

The main positive experiences are as follows:

- What is particularly highlighted by clinicians across the 13 patient groups is the **increased formalised and informal collaboration** between and across specialties. Whole genome sequencing requires expertise from different medical disciplines, and the national implementation has fostered **closer collaboration between specialists in a wide range of medical specialities**. This multidisciplinary approach creates a platform for sharing experiences and optimising patient care across disciplines. This particularly includes **new collaborations and multidisciplinary teams** (MDTs) that have emerged between clinicians, geneticists and interpreters where complex patient cases are discussed and assessment and treatment plans are coordinated to **ensure more precise and individualised treatment strategies for the benefit of the patient**. The specialist networks also highlight increased national collaboration organised regionally or through medical societies. One example is GenNets under the Danish Society of Medical Genetics, which works to promote knowledge sharing and national uniform clinical management of patients and families at risk of developing a genetic disease.

- The implementation of whole genome sequencing, including ensuring **national access to advanced diagnostic technology** across regions and patient groups, has contributed to **increased equality for patients.** All patients will have equal opportunities to benefit from whole genome sequencing, regardless of their geographical location.

- Whole genome sequencing has **important technological advantages** compared to other methods because it sequences all parts of the genetic material, including both the coding and non-coding regions. The broader coverage allows for increased detection of rare and structural variants, as well as variants in 'new' genes, resulting in **more patients receiving a genetic diagnosis.** However, clinicians believe that the added value of whole genome sequencing over exome sequencing is currently relatively limited, as the analysis focuses on known disease genes and there is still relatively limited knowledge about the disease impact of variants outside the coding regions. Nevertheless, it contributes to a more comprehensive understanding of genetic variants and disease risks, which is crucial for developing personalised medicine.

- A significant advantage of whole genome sequencing and genome storage is also the **ability to reanalyse patient data** at a later stage in light of new knowledge. This ensures that diagnostic results can be continuously updated and refined to the benefit of both patients and the healthcare system.

- It matters to clinicians to be able to **offer patients the best available diagnostics** from the outset, thereby avoiding a potentially lengthy assessment process with repeated (less comprehensive) tests in some cases.

- The creation of a national platform for analysing whole genome sequencing is a necessary structure for effective implementation. The platform has **facilitated data exchange, standardisation of processes and coordination of national initiatives**. It serves as a centralised resource that facilitates collaboration between healthcare providers, laboratories and research institutions.

- The specialist networks would like to emphasise that whole genome sequencing for the selected indications is **clinically relevant and that patients benefit greatly from the programme**. From a medical perspective, **the programme cannot be rolled back** – also because technological advancements, including the use of whole genome sequencing, in **Denmark follow the development internationally**. During the interviews, it was argued that patient organisations are unlikely to accept the rollback of a technology that has proven to be of great importance for patient diagnostics and treatment.

"Denmark follows the development internationally"

- The potential of whole genome sequencing is not necessarily realised immediately, but rather over time. **Technological developments, research and clinical experience will help to continuously improve its application and effectiveness.** For this reason, it is important to be aware that although **positive results are already evident, there is still untapped potential** that is expected to grow in the future. There is a great need for additional opportunities to share data. **National databases and international collaborations are essential** to gain greater insights and improve our understanding of genetic variations across populations. This requires investments and technology platforms that **enable secure and standardised data sharing**.

While emphasising these positive aspects, it is also important to address the unfavourable aspects that have been highlighted in connection with the implementation of whole genome sequencing nationally:

- A key point is that **national implementation of whole genome sequencing takes time**, and it is important to recognise that it is a **gradual process**. This has required (and continues to require) significant investment in organisation, training and infrastructure for handling data. This means that the full effect of the implementation has not yet been realised.

- Another major challenge is **the increased response time** that patients experience due to an increasing number of tests and lack of resources for interpretation. This may delay diagnosis and treatment decisions, potentially negatively impacting the patient experience and outcomes.

- There is an urgent need to address the **shortages of physicians, bioinformaticians and interpreters** in comprehensive genetic diagnostics. **Training and capacity building is necessary** to meet the growing demand for specialised expertise in this field. This includes not only training existing healthcare professionals, but also attracting and training new professionals.

- **The logistics of requisitioning and patient consent are described as a significant challenge** across patient groups. Ensuring a smooth process from sample collection to analysis requires effective coordination and well-defined procedures. Some regions have implemented **electronic solutions**, such as consent forms, to reduce the amount of paper forms for whole genome sequencing. Other regions have not had the same electronic solutions, thus facing a greater administrative burden when providing whole genome sequencing. Efficient systems and technological solutions should be implemented to reduce the manual workload and improve process efficiency.

- During the interviews, some specialist networks stated that they have observed an increased occurrence of variants of unknown significance, while other networks stated that they have observed fewer of these variants than expected.

Finally, the specialist networks have expressed a desire for additional diagnostic and follow-up options.

- Expansion to increase diagnostic yield:
  - Expanding the diagnostic tools so that other additional analyses can eventually be omitted, e.g. in the form of better detection of so-called repeat diseases based on whole genome data.
  - RNA sequencing in certain cases for rare hereditary diseases.
  - Deeper sequencing when testing for mosaic conditions.
  - Access to Danish frequency and variant databases.
  - Improved linking of multiple data sources.
  - Possibility of sequencing of deceased persons.

- Requests for further follow-up:
  - Systematic collection of data for prospective clinical studies.
  - Calculation of the total time before the patient receives a response.
  - Evaluation of the regions' implementation of whole genome sequencing.

Conclusions on national experiences

"Therefore, patience and sustained commitment is an important prerequisite for successful implementation of whole genome sequencing at national level."

Across the 13 patient groups, interviews with clinicians describe how the national implementation of **whole genome sequencing has had a significant impact on the diagnosis and treatment of patients** and is now a systematic part of patient assessments nationally. **More patients are being genetically tested and diagnosed**, which is important for patients and allows for **individualised follow-up and treatment**. The use of whole genome sequencing can save both the patient and the healthcare system many additional examinations and/or visits/consultations by avoiding repeated tests and diagnosing conditions more accurately at an earlier stage. This not only **streamlines diagnostic processes**, but also **reduces healthcare costs** in a long-term perspective.

The national implementation has **greatly promoted interdisciplinary collaboration** at local, regional and national levels and has increased focus and knowledge about genetic testing. Whole genome sequencing has **technological advantages, and storing genomes in a national database enables reanalysis of patient data, which can save time and resources. Implementation challenges include a lack of resources,** especially for interpretation, which has led to **increased response times** in some locations, logistical challenges in requisitioning and impractical consent procedures.

Overall, it is assessed that the full effect of the implementation has not yet been realised, but that it will materialise over time. Therefore, **patience and sustained commitment** is an important prerequisite for successful implementation of whole genome sequencing at national level.

International perspectives highlighted by systematic literature reviews

Together with the specialist networks, the Danish National Genome Center (NGC) has conducted systematic literature reviews for each patient group with the aim of gathering international insights into the clinical effect of whole genome sequencing for the patient group. Each literature review is based on references from the specialist network and searches in the PubMed database for the latest scientific literature. The method is inspired by a recognised model for systematic literature review (PRISMA) and adapted to the current purpose. The literature review for the 13 patient groups includes a total of 106 unique publications that highlight the latest international knowledge on the clinical effect of whole genome sequencing for diagnosing rare hereditary diseases.

Overall, the included literature is considered to be representative of the 13 patient groups with rare hereditary diseases who are given access to whole genome sequencing under the auspices of NGC, and to illustrate the clinical effect of whole genome sequencing in patients, see Table 2.

Patient group	**Included literature representative of the patient group**	**The included literature sheds light on the clinical impact of (comprehensive) genetic diagnostics**	**International clinical guidelines/expert opinions on (comprehensive) genetic diagnostics**
Inherited cardiac disease	Yes	Yes	Yes
Hereditary haematological disease	Yes	Yes	Yes
Hereditary cholestatic and fibrotic liver diseases	Yes	Partially	Not covered by the included articles
Audiogenetics	Yes	Yes	Not covered by the included articles
Endocrinological patients	Yes	Yes, generally	Yes
Foetal medicine	Yes	Yes	Yes
Neurogenetic patients	Yes	Yes	Yes
Kidney failure	Yes	Yes	Yes
Ophthalmology	Yes	Yes	Yes
Primary immunodeficiency	Yes	Yes	Not covered by the included articles
Psychiatry, children and adolescents	Yes	Yes	Yes
Rare diseases in children and adults	Yes	Yes	Yes
Severe hereditary skin diseases	Yes	Partially	Yes

Table 2 summarises the systematic literature reviews for the 13 patient groups.

In the following, we first summarise the positive aspects of comprehensive genetic diagnostics in patients with rare hereditary diseases, followed by typical limitations or challenges in the field as described in the literature:

- Across the 13 patient groups, the systematic literature reviews show that **comprehensive genetic testing plays a key role in ensuring diagnostic clarification in patients with rare hereditary diseases**, which is essential for providing patients with individualised treatment and follow-up.

- The 13 patient groups include many different and individually rare conditions that share the common trait of a suspected underlying genetic cause. Many are serious, complex and lifelong conditions that can involve multiple organ systems. Several conditions have overlapping manifestations that are difficult to distinguish clinically, or they may present suddenly or unexpectedly where early preventive action could have potentially prevented or mitigated the course of the disease. Against this background, (comprehensive) genetic assessments are described as having a pivotal role in the diagnostic clarification of patients with rare hereditary diseases, providing a **timely and accurate (genetic) diagnosis, which is crucial for proper treatment and follow-up of patients**. Consistent with this, **international clinical recommendations** for the use of (comprehensive) genetic diagnostics exist for a wide range of rare hereditary conditions. These recommendations come from international medical societies and expert groups[11–17] as well as European reference networks for rare diseases[18–20] .

- A significant clinical effect of a genetic diagnosis is the diagnostic clarification of the often complex and serious conditions. This ensures **an end to what is often a years-long diagnostic odyssey** and provides an explanation of the condition to the patient/family. An accurate diagnosis **also prevents further unnecessary and potentially harmful examinations and treatments**. A genetic diagnosis also has prognostic significance, for example in predicting the development or severity of the disease, the expected effect of a procedure/treatment, or the risk of developing further disease not known at the time of diagnosis, such as symptoms from other organ systems or risk of cancer that indicates a need for follow-up.

- In a significant proportion of patients with rare hereditary diseases, **a genetic diagnosis** is described as **having therapeutic implications** in terms of ensuring timely and correct clinical management, including individualised follow-up and (possibly targeted) treatment. **For example, a recent large meta-analysis found a clinical effect in 61-77% of patients with rare diseases** where a genetic diagnosis made by whole genome sequencing led to **changes in the clinical management of patients. Furthermore, the clinical effect increased over time**[1]. In addition, increasing opportunities for targeted therapy are being described, including access to clinical trials, some of which involve gene therapy, where inclusion requires genetic diagnostics. This means that the importance of genetic diagnostics is expected to increase further in the future.

- A genetic diagnosis extends beyond the individual patient as it **allows for genetic counselling, including information on recurrence risk and reproductive options such as prenatal genetic testing and Preimplantation Genetic Testing (PGT).** In addition, there is the possibility of **genetic testing offamily members, including the identification of relatives at risk** who need follow-up (e.g. for cancer), as well as clearance of relatives who thus do not need follow-up. **The possibility of genetic testing in relatives is particularly emphasised in cases where organ donation (e.g. kidney or liver) within the family is being considered.**

- The literature describes that the diagnostic yield varies significantly within and across patient groups and indications, depending on the specific population/indication and method, making cross-comparisons difficult. In general, however, **diagnostic yield** is described **to be higher** when using more comprehensive genetic testing such as whole exome or whole genome sequencing for comparable indications, compared to standard genetic testing (e.g. chromosomal microarray, single gene analysis or gene panel), due to technological superiority. It also describes a **tendency for the diagnostic yield to increase over time, which is related to scientific and technological advancements**, including the discovery of new genes and increased knowledge of disease mechanisms.

- Across patient groups, the literature emphasises the difficulty of assessing effect in rare hereditary diseases. Most studies include only a few patients and/or very heterogeneous patient groups, and there are few or no randomised controlled trials, which makes it difficult to uniformly assess diagnostic yield or clinical effect across studies/patient groups. Consequently, the literature highlights a general **need for uniform assessment of effect and further research** to improve diagnostics and treatment of patients and contribute to the development of new treatment modalities in the long term.

- Overall, the literature supports the potential of comprehensive genetic diagnostics such as whole genome sequencing to **improve health and quality of life of patients** with rare hereditary diseases. However, there is a need for standardisation/harmonisation and research to clarify the actual clinical effect.

- Finally, it should be noted that the clinical effect of whole genome sequencing described in **the international literature correlates with the clinical effect for the Danish patients/patient groups**, which supports that experiences from the literature can help illustrate the clinical effect of whole genome sequencing in Danish patients.

International experience with the use of whole genome sequencing in comparable countries

The Danish National Genome Center (NGC) has summarised the use of whole genome sequencing for the patient groups in England, France and Sweden to highlight overlaps in the use of whole genome sequencing for the selected indications under each patient group (Table 3). England, France and Sweden were chosen as they provide whole genome sequencing in a public setting. There are many similarities in the use of whole genome sequencing between these three countries and Denmark, where many of the same patients are offered whole genome sequencing. The individual countries have comparable procedures for how they each include new disease indications or patient groups for whole genome sequencing (Table 4).

Patient group	**Comparison of indications internationally**
Inherited cardiac disease	Full overlap
Hereditary haematological disease	Full overlap
Hereditary cholestatic and fibrotic liver diseases	Some overlap
Audiogenetics	Full overlap
Endocrinological patients	Full overlap
Foetal medicine	Small overlap
Neurogenetic patients	Full overlap
Kidney failure	Full overlap
Ophthalmology	Full overlap
Primary immunodeficiency	Good agreement
Psychiatry, children and adolescents	Full overlap
Rare diseases in children and adults	Full overlap
Severe hereditary skin diseases	Full overlap

Table 3: Comparison between the use of whole genome sequencing internationally and under the auspices of NGC.

Country	Inclusion of patient groups
Denmark	Recommendation rounds with review by the working group on clinical applications of whole genome sequencing under NGC and approval by the steering committee for implementation of personalised medicine.
England	England has a National Genomic Test Directory for both rare diseases and cancer that details all genetic tests offered in the National Health Service (NHS). Any requests for expansion/modification of this directory are dealt with by the Genomics Clinical Reference Group and test evaluation working groups under Genomics England and NHS England following a structured, evidence-based process.
France	Recommendations are processed by the French initiative (Plan France Médecine Génomique) and the French health authorities (Haute Autorité de Santé).
Sweden	Development of clinical guidelines

Table 4: Comparison of procedures for including new disease indications or patient groups for whole genome sequencing.

Summarising international experience with the use of whole genome sequencing in comparable countries shows that:

- overall, there is almost **complete overlap between the Danish indications** and the indications eligible for whole genome sequencing in comparable countries such as England, France and Sweden, see Table 3.

- **the large international overlap is probably due to relatively similar clinical criteria** for when a patient should be offered whole genome sequencing as part of their assessment/treatment.

- however, there are a few exceptions in the foetal medicine patient group, where only limited whole genome sequencing is offered internationally. The specialist network for foetal medicine notes that this is because **Denmark is very advanced** in this field. For the hereditary cholestatic and fibrotic liver diseases patient group, there is only some overlap in the use of whole genome sequencing internationally.

Summary of interviews with patient representatives

On 20 March 2024, NGC held a semi-structured interview with the participation of 9 patient representatives from the national specialist networks, the advisory board for patients, citizens and ethics and associations under Danish Patients, including: the Danish Ataxia/HSP Association, the Danish Wilson Patient Association, Rare Diseases Denmark, the Danish Cancer Society, the Danish Association for Children with Cancer, the Danish Muscular Dystrophy Foundation and the Danish Rehabilitation Centre for Neuromuscular Diseases, Osler/HHT Denmark, the Danish Epilepsy Association and the Danish Kidney Association. The purpose was to elucidate the patient perspective on the implementation of whole genome sequencing. Below is a summary of the most important points from the interview. The full transcripts of the interview with the patient representatives have been approved by the participants and are available upon request from NGC.

The interview with the patient representatives provided in-depth and nuanced insights into their experiences, concerns and hopes in relation to whole genome sequencing, including:

- Several participants shared personal stories of **how whole genome sequencing had been instrumental in providing correct diagnoses** and offering targeted treatment, which had a significant positive impact on their quality of life and prognosis.

- It was argued that the access to **whole genome sequencing can be expected to lead to earlier diagnosis**. It was agreed that this is very important, as an early diagnosis can facilitate early intervention and prevention to minimise disease progression.

- Concerns were expressed that **if the whole genome sequencing programme is cancelled, patients will (again) have to wait longer for a diagnosis**, or might not be able to receive a diagnosis and consequently the right treatment.

- At the same time, challenges were addressed, particularly in relation to communication and understanding among patients, especially in acute situations after a new diagnosis. Many patient representatives emphasised the importance of **information from healthcare professionals being tailored to the individual needs of patients and their current life situation**. One example described the intense emotional strain experienced by parents of acutely ill children, including children with cancer, who are often in a state of shock, where it can be difficult to absorb and understand the information given, for example about whole genome sequencing. This highlighted the need for a personalised approach from healthcare professionals.

- In addition, concerns were raised about **the resource needs of the healthcare system**, both in terms of sufficient time for follow-up after diagnosis and access to the right medication. Another important aspect was dealing with the potential psychological and financial consequences for the patients.

- Despite the challenges, the consensus was **that whole genome sequencing has the potential to revolutionise patient care**. Participants called for continued focus on **systematic patient involvement in decision-making processes**, including a focus on individual patient needs and wishes and a coordinated approach at national level to ensure optimal utilisation of whole genome sequencing.

- ·In addition, there were also reflections on how to better manage the dialogue between patients and healthcare professionals about secondary findings, including creating more effective systems to ensure **personalised follow-up and communication between healthcare professionals and individual patients.** Several participants emphasised the importance of creating a safe and information-rich environment for patients where they feel supported and well-informed throughout the process.

It was also argued that **when treatment is available, it should be offered.** The Danish Medicines Council regularly reject treatment options due to costs.

Summary of interviews with members of the working group on clinical applications of whole genome sequencing

On 29 April 2024, NGC conducted a semi-structured interview with seven members of the working group on clinical applications of whole genome sequencing. The purpose was to get the working group's overall perspective on the experiences described in the status reports for the 17 patient groups. During the interview, additional points related to the national experiences described were highlighted. The interview summary has been approved by the participants and is available on the NGC website.

- The working group indicated that **regulatory constraints in the field** prevent the application of lessons learnt from one patient to the next. This makes learning difficult, including optimising diagnostics and treatment based on the programme.

- The working group emphasised the **need to measure and quantify the effect of the programme** to facilitate any concrete statements about the effect of the programme for patients.

- The working group found that in some areas, whole genome sequencing **has replaced several previous, less comprehensive genetic analyses,** potentially **shortening the diagnostic process**. It was emphasised that when implementing new methods, there is a need to evaluate the effect in relation to existing methods so that any **unnecessary analyses can be suspended**.

- The working group discussed potential **savings from the use of whole genome sequencing** that are deemed relevant across the patient groups, including **simplifying laboratory and/or clinical workflows and ending often lengthy diagnostic odysseys**. In addition, potential **future applications in areas such as pharmacogenetics and prevention can ensure timely, targeted treatment** – with significant benefits for both patients and the healthcare system.

- Operational considerations included **concerns about transitioning to local/regional budget responsibility**. One of the concerns was that if the joint national funding stops, it will mean **the end of equality for patients nationally**, as access to whole genome sequencing would then be limited to some patients or only be available through (foreign) research projects, for instance. Some saw **whole genome sequencing as an economic benefit to society, bringing otherwise 'invisible' patients with rare diseases further ahead in the queue.**

- The working group believed that there is **no realistic alternative to whole genome sequencing**, as the technology is used internationally and offers great advantages. **A cancellation of the national programme would create unequal access and limit research**.

- The working group expects **the use of comprehensive genetic analyses to increase**, also for new indications such as pharmacogenetics, and prediction/polygenic risk scores. **Technology is becoming cheaper** all the time, and better tools for interpretation and automation are being developed. In addition, **the yield can be increased by reanalysing data regularly** as new insights emerge.

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