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Lessons learnt from national implementation of whole genome sequencing

PATIENT GROUPS WITH CANCER

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

Summary

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 deemed likely 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 describes the overall lessons learnt from the implementation of whole genome sequencing across the **four patient groups with cancer**, including hereditary cancer. For these groups, **6,693 samples have been sequenced** since the inception in 2022, with a process time of 17 days. The lessons from the 13 patient groups with rare hereditary diseases 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 four patient groups with (hereditary) cancer, the programme is of great importance to patients and clinicians in terms of **better patient pathways and better and faster diagnostics and treatment**. In addition, there is the issue of **clarification of heredity**, where the diagnosis of patients with hereditary cancer has implications that extend into the family. 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**. Both clinicians and patient organisations consequently want the use of whole genome sequencing to continue, as it **provides technological advantages that can streamline diagnostic processes and is a natural step in the development** 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 is expected to further materialise over time**, partly due to the possibility of re-analysis of data and in line with technological and knowledge developments, including preventive and predictive applications.
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.

For example, Aarhus University Hospital has received funding for a development project comparing standard diagnostic assessment and whole genome sequencing for patients with haematological cancer. Preliminary analyses and experience show that the setup works as hoped, with the possibility of obtaining a full response within a **clinically relevant response time of approximately 8 days**. At present, the project has found **good correlation between whole genome sequencing and standard diagnostic assessments** and made several findings that are crucial for clinical decisions and reassessment of individual patients' prognosis compared to standard assessments.

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 cooperation at national level** and has contributed to **competence building** broadly in terms of knowledge and use of advanced genomic diagnostics, as well as standardisation. 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 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 four patient groups, show that access to **comprehensive genetic diagnostics is central to ensuring accurate diagnosis and classification** of genetically driven diseases such as (hereditary) cancer. The results help **guide treatment decisions and ensure individualised or targeted treatment and follow-up for a significant proportion of patients**, which will increase treatment effectiveness, reduce side effects and ultimately improve patient survival. In hereditary cancer, an accurate diagnosis also ensures that follow-up is (only) offered to relevant persons at risk in the family. The central importance is underlined by international clinical recommendations in this area. The **technological advantages of whole genome sequencing are crucial for facilitating an accurate diagnosis for more patients compared to standard genetic testing**. At the same time, increasing diagnostic yields are reported over time and are expected to increase further as knowledge and technology advances and new treatment options are developed. Another important point is that t**he effect of whole genome sequencing described for the Danish patients/patient groups aligns with international experiences** and that the programme offered to the four Danish patient groups is consistent with programmes in comparable countries, indicating that **Denmark with the programme is in line with international developments. The use of whole genome sequencing is expected to expand in line 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 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, as stated above, there is experience with the clinical use of whole genome sequencing for disease areas that overlap with the Danish patient groups with cancer including hereditary cancer**. In addition to clinical effect, these experiences also assess technical and health economic perspectives. For example, a number of studies observe a higher diagnostic yield/proportion of variants for which targeted treatment is available [MBR1] through comprehensive genetic testing such as whole genome sequencing, compared to standard genetic testing in people with cancer, and the yield has been **increasing over time**. In addition, there are emerging indications that the use of **whole genome sequencing as a first choice may be cost-effective** 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 with rare diseases and cancer 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 report aims to provide an overview of the lessons learnt from the national implementation of whole genome sequencing for the four patient groups that include patients with cancer, including hereditary cancer, who are currently being offered whole genome sequencing as part of their treatment. A similar consolidated report has been prepared for the 13 patient groups with rare hereditary diseases.

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 (four 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 four patient groups that include patients with cancer, including hereditary cancer:

1. Haematological cancer
2. Childhood and adolescent cancer
3. Cancer in young adults and hereditary cancer in adults
4. Disseminated and incurable cancer

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 summarises the overall lessons learnt from the status reports for the four patient groups with cancer, including hereditary cancer, 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 four 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 well established, 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.

Despite the different starting points, there are overlapping experiences from the national implementation of whole genome sequencing in the four 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. In the cancer patient groups, the diagnostic assessment may include sequencing of blood sample, tumour and RNA sample. In addition, some patients need a family test, with trio-analysis of child + parents. NGC is not able to distinguish the proportion of blood, tumour, RNA and family samples in the total number of samples. However, the total number of patients examined can safely be assumed to be lower than the number of samples sequenced for the patient groups.
The national specialist networks for the four patient groups with cancer, including hereditary cancer, have reported an annual requirement of 12,800 samples for newly referred patients. Since the patient groups started in 2022, 6,693 samples have been sequenced for the four 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 August 2022 and April 2024, 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 four patient groups is relatively stable at approximately 400 samples per month, corresponding to approximately 4,800 per year (Figure 1). However, a slight increase in the number can be observed over the last six months. Over the last six months (1 November 2023 – 1 May 2024), the total sequencing has corresponded to 38% of the reported number of samples for newly referred patients.

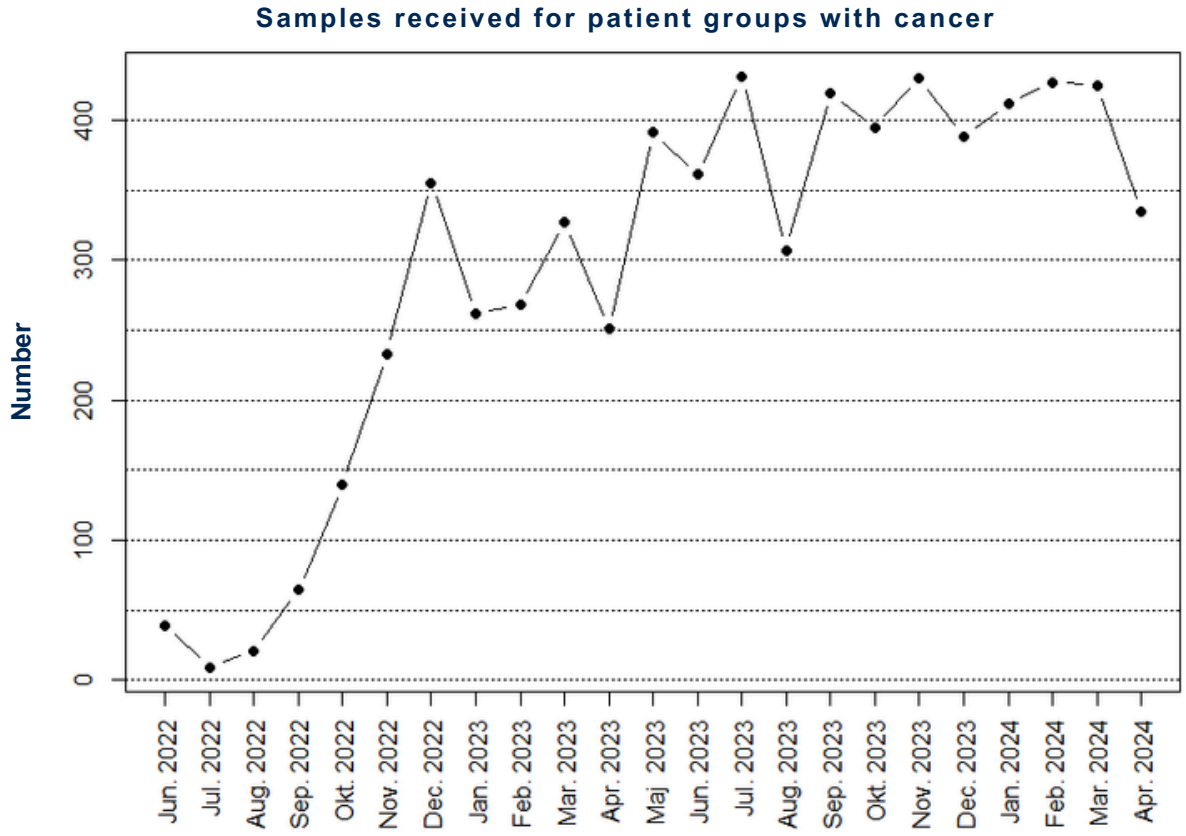

Figure 1 shows the development in the number of sequenced samples for the four patient groups that include patients with cancer, including hereditary cancer.

Table 1 shows the number of samples submitted for each of the four 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 9% to 75%.

Patient group	**Total samples**	**Percentage submitted for newly referred patients November 2023 to May 2024**
Haematological cancer	180	41%
Childhood and adolescent cancer	1002	75%
Young adults with cancer and hereditary cancer	422	9%
Disseminated and incurable cancer	5089	44%
Total	6693	38%

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.

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.

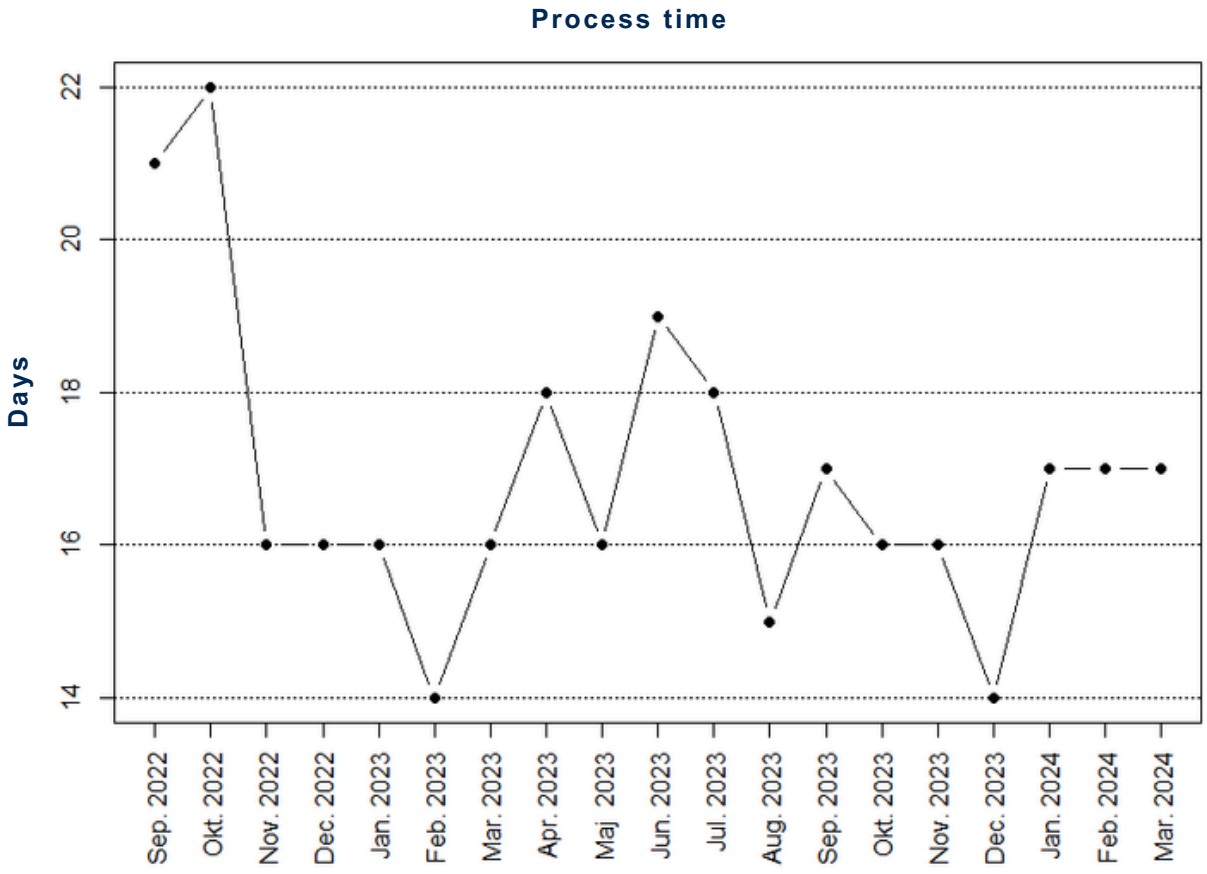

Figure 2 shows the monthly process time for 90% of all samples for the 17 patient groups in the period September 2022 to March 2024.

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 four patient groups has been **a comprehensive 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 and partly standardise 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 has not yet been fully implemented for several 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 assess that fewer patients than expected meet the criteria described, while others believe that the original delimitation was perhaps too narrow, given the rapid developments in the field. Finally, some specialist networks report that some patients/families **decline the examination or that the examination cannot be performed for other reasons (e.g. due to the need for (new) biopsy)**. In addition, due to the large number of samples, **resources for interpretation have turned out to be insufficient**. For some patient groups, this has led to a practice where you **may start with less comprehensive genetic analyses in some cases, resulting in fewer samples subsequently being submitted for whole genome sequencing**. Finally, it is assessed that (minor) differences in the diagnostic approach, as well as differences in financial settlement models, may have had an impact on ordering patterns/number of tests.

The specialist networks also report that the implementation of the national whole genome sequencing programme for the four patient groups **represents a significant and important technological advancement that should continue** due to its major importance for patients and clinicians, which is expected to increase in the future.

> “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 (hereditary) cancer. This provides clarity for patients and their families and has the potential to improve the quality of life through individualised or targeted treatment and follow-up.
- 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 and logistical challenges** regarding requisition and consent.
- In addition, the need for linking and collecting data (e.g. in databases) and access to targeted medicines are also mentioned as limiting factors when it comes to the effect of precision medicine. Overall, the need for continued investment and commitment to realise the full potential is highlighted.

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

- Comprehensive genetic diagnostics such as **whole genome sequencing plays a key role in ensuring diagnostic clarification in genetically driven diseases such as cancer, including hereditary cancer**, thereby ensuring individualised or targeted treatment and follow-up for patients and possibly their families.
- **Diagnostic yields are increasing over time** and are expected to increase further as knowledge and technology advances and new treatment options are developed.
- 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 in patients with cancer, including hereditary cancer, 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 experience 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 groups, the specialist networks have submitted a total of 15 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 **contributes to diagnostic clarification** and an explanation of the condition, which holds great importance for patients and in some cases **brings an end to lengthy diagnostic processes** that are stressful for the patients/families and could have been avoided.

- Whole genome sequencing can contribute to **improved diagnostics** in the form of new knowledge, for example in cases where standard examinations are without findings or **where the genetic defect could not be detected by other methods.**

- An accurate genetic diagnosis provides diagnostic and prognostic certainty that **supports clinical decision-making, for example**:
  - A genetic diagnosis has therapeutic implications, including individualised treatment strategies in the form of **(targeted) treatment, possibly access to clinical trials** or planning of procedures such as bone marrow transplantation.
  - Whole genome sequencing of tumour tissue can provide **improved risk classification** as well as information on expected efficacy or resistance to (targeted) treatment, thereby **guiding treatment decisions**. In addition, cancer progression can be monitored, allowing for adapted treatment which provides patients with more quality years of life.
  - Planning **long-term follow-up**, such as a control programme for patients with a congenital hereditary (germline) predisposition associated with an increased lifetime risk of cancer.

- A germline predisposition can explain any **syndromal symptoms** that extend beyond the cancer diagnosis, thereby ensuring **relevant follow-up**. Another example describes how a secondary finding of a progressive hereditary metabolic disease allows for **early initiation of relevant, targeted treatment**.

- A germline predisposition allows for **genetic testing of family members** , including identification of relatives at risk, enabling early detection and treatment if they develop cancer. Genetic testing in relatives is also highlighted in cases of bone marrow transplantation, where family members are considered as donors.

- In some cases, a genetic diagnosis can result in **suspicions of heredity being disproved**, just as a normal result can be associated with relief for the patient/family, for example if suspicions of a high-risk condition can be disproved.

- Some cases describe **increased collaboration and knowledge sharing** as a result of the national programme, for example in one case where the established national collaboration contributed to **diagnostic clarification of cancer in children**, enabling relevant follow-up and genetic testing in relatives.

National experiences from interviews with clinicians

In January 2024, semi-structured interviews were held with all four 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 cooperation.

The main positive experiences are as follows:

- Across the four patient groups, clinicians emphasise that the use of whole genome sequencing is **of great importance to the patient group** in relation to the assessment and (targeted) treatment of patients, including in relation to **determining the treatment strategy and possibly opening up new treatment options**.

- Offering whole genome sequencing as the first-line analysis can help **shorten the time to diagnosis**, for example by **replacing previous diagnostic odysseys** of repeated analyses with one analysis, reducing anxiety for patients and their families due to faster clarification.

- Whole genome sequencing can provide **knowledge about heredity** in the form of a congenital (germline) predisposition, which is important for **targeted treatment options**, and further enables geniting testing of family members and possible reproductive choices.

- Whole genome sequencing offers **technological advantages** compared to e.g. gene panels and exome sequencing, which provide important data about for example structural variants and variants outside the coding areas (introns). The broader coverage of whole genome sequencing can contribute to **more patients receiving a genetic diagnosis**. However, there is currently no data from Danish patients that can be used to assess the potential added value of whole genome sequencing compared to previous genetic testing-strategies.

- One perspective that was highlighted by the specialist networks is that collecting data from whole genome sequencing has **great future potential**, such as the possibility of examining data beyond the disease genes currently known or beyond what is merely monogenic (so-called **polygenic risk scores**). Also, the ability to **reanalyse patient data** at a later date in the light of new knowledge was highlighted as **an important aspect of storing whole genome data.**

- Across the four patient groups, clinicians emphasise that the establishment of the national programme has been of great importance in terms **of increased knowledge, collaboration and standardisation**, e.g. in relation to national diagnostic strategies. The uniform whole genome sequencing programme, where the same data is analysed in a uniform way, provides **a common platform that supports national knowledge sharing** and facilitates collaboration across departments and regions and contributes to equality in healthcare. Interdisciplinary collaboration has been strengthened in the form of multidisciplinary teams (MDT) or national tumour boards. **Overall, the increased collaboration contributes to improving the quality of the results, enhancing diagnostics and treatment for patients.**

- The national implementation and data from whole genome sequencing have strengthened **international collaborations** and play an important role in relation to Denmark's future **participation in international research and treatment/clinical trials.**

- Across patient groups, there is broad agreement that whole genome sequencing for **the selected patient groups is clinically relevant** and that Denmark is keeping up with technological developments. This is is emphasised by the fact that **the Danish programme is in line with international programmes** in the European countries we normally compare ourselves with. Accordingly, clinicians emphasise that rolling back access to whole genome sequencing risks delaying the assessment of patients and limiting access to new treatments. One specialist network puts it this way: "cutting access to whole genome sequencing (and similar analyses such as exome sequencing) for patients effectively corresponds to blocking the highway for precision medicine in Denmark."

“The Danish programme is in line with international programmes”

- Clinicians state that the implementation can be seen as part of a development phase, both technically and therapeutically, which is why the **potential for whole genome sequencing is not necessarily realised immediately, but rather over time.** At present, there are no reports that can be used to illustrate the potential added value of whole genome sequencing compared to previous genetic testing, as local experiences and data are still being gathered and analysed.

- **Systematic data collection and linkage between clinical and genetic data**, as well as improved opportunities for research, are important prerequisites for realising the full potential of whole genome sequencing in clinical practice.

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:

- The process of implementing the programme has been **cumbersome and time-consuming**, and some parts have been **surprisingly difficult to implement**, such as a common somatic pipeline. Also mentioned is the desire to realise **parts of the ambition that have not yet been realised, such as quality databases** and variant classification databases. Similarly systematic data collection, for example to document the effect, was highlighted as important in order to tap into the full potential of the implementation. A key point is that **implementing whole genome sequencing nationally is a gradual process** that has required (and continues to require) **significant investment in organisation, training and data management infrastructure.**

- Interpretation of comprehensive genetic tests such as whole genome sequencing is complex and has resulted **in an increased workload for interpreters,** which needs to be addressed. **More resources are needed for interpretation**, including **training and competence building** in a broad sense. There is also a need **to strengthen communication** about the opportunities and limitations of comprehensive genetic analyses, both between patient and clinician and in the general population.

- Some clinicians mentioned **barriers** related to the less-than-expected ordering of whole genome sequencing in some areas, including **finances such as interpretation costs. Response** time is also mentioned as a barrier within some patient groups/indications in terms of obtaining the results of whole genome sequencing within a clinically relevant time frame.

- Across patient groups, the process of obtaining **consent is described as resource-intensive, and the effort is not considered to be commensurate with the outcome**. Among other things, there is believed to be a very large focus on secondary findings in the consent compared to the clinicians' experiences of how much secondary findings actually mean in everyday life. There is a need to **evaluate the consent process**, for example involving international experience.

- Within some patient groups, **access to targeted medicines was highlighted as limiting in terms of the efficacy of precision personalised medicines.** The barriers are described partly as a general lack of development of medicinal products targeted at genetic variants and partly as **a lack of (real) access to targeted medicinal products, e.g. conditional on procedures for the authorisation of medicinal products.**

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

- Expansion to increase diagnostic yield:
  - Possibility to examine data beyond monogenic conditions (i.e. so-called polygenic risk scores).
  - Optimised somatic pipeline nationally.
  - Access to Danish frequency and variant databases.
  - A Danish clinical trials database.
  - Better linking of multiple data sources (clinical, genetic and research data).
  - Improved data sharing and the ability to conduct research in data.
- Requests for further follow-up:
  - Systematic data collection for prospective clinical studies, e.g. via quality databases.
  - 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 four patient groups, clinicians emphasise the **crucial role of whole genome sequencing in diagnosing and treating patients with cancer**, including opening up **new treatment modalities** and providing important knowledge about heredity. Whole genome sequencing as the first analysis has the potential to **shorten the time to diagnosis** by replacing several existing analyses, and its technological superiority contributes to **improved patient diagnostics**. This not only streamlines diagnostic processes, but **also reduces healthcare costs** in a long-term perspective.

The national implementation has been of great importance in terms **of increased knowledge, collaboration and standardisation**, and contributed to **equality in health as well as improved diagnostics and treatment of patients**. Challenges include a **resource-intensive implementation process and increased workload** for interpreters, underlining the need for training and competence building. Also, **long response times** limit the use of whole genome sequencing in certain patient groups. Finally, there is a need for **evaluation of the consent process.**

Overall, the consensus is that offering whole genome sequencing to the selected patient groups is **clinically relevant and in line with programmes in other countries**. However, the effect of the implementation has not yet been fully realised. Realising the full potential requires **systematic data collection**, e.g. in databases, and better linking of data. There is also great future potential in the possibility of including new knowledge and predictive use, for example in the form of so-called polygenic risk scores. Therefore, **patience and sustained commitment** is an important prerequisite for successful implementation of new technologies 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 four patient groups includes a total of 15 unique publications that highlight the latest international knowledge on the clinical effect of whole genome sequencing in cancer, including (suspected) hereditary cancer. In relation to cancer, genetic diagnostics generally involves two different diagnostic approaches: somatic analysis for acquired variants in tumour tissue, having treatment implications for the patient, and germline analysis of normal tissue for an underlying hereditary predisposition, having health consequences for both the patient and potentially for relatives. The literature review included both of these applications in patients with cancer.

Overall, the included literature is considered to be representative of the four patient groups with (hereditary) cancer 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
Haematological cancer	Yes	Yes	Yes
Childhood and adolescent cancer	Yes	Yes	Yes
Young adults with cancer and hereditary cancer in adults	Yes	Yes	Not covered by the included articles
Disseminated and incurable cancer	Yes	Yes	Yes

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

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

- Cancers are described as **genetically driven diseases** characterised by significant genetic complexity and heterogeneity. The four patient groups include many different types of cancer, including (often rare) hereditary cancers, which together are associated with significant morbidity and mortality, both relating to the primary cancer and any subsequent (cancer) disease.

- Against this background, the literature emphasises **genetic diagnostics as central to correct diagnosis and risk stratification, with implications for treatment.** Consistent with this, WHO classifications for conditions such as brain tumours and haematological cancer include genetic diagnostics, and international medical societies and expert groups recommend comprehensive genetic diagnostics, including whole genome sequencing[10,11].

- A significant clinical effect of genetic diagnostics in patients with cancer is **diagnostic clarification**. Analysis for somatic variants can contribute to **diagnosis, classification, risk stratification and prognostication**, as well as **guide treatment decisions**, for example by predicting the response (or resistance) to chemotherapy or targeted therapy. **Multidisciplinary specialised collaboration**, for example in the form of molecular tumour boards (MTB), appears to improve outcomes for cancer patients. For example, a systematic review found clinical effect of MTB-recommended targeted therapy in 42-100%, and in one study patients obtained **significantly better survival than patients** in the control group receiving standard treatment[3]. In a large study of patients with advanced cancer, whole genome sequencing found off-label indications for registered targeted medicinal products in 8%. A follow-up study on alternative use of authorised medicinal products (drug repurposing) **included 50% of patients based on whole genome sequencing**, which clinically benefited one in three patients[1] .

- The finding of a germline predisposition is described as crucial for **diagnosis, risk assessment and prognosis in patients and their relatives** due to increased lifetime risk of cancer and risk of cancer at a younger age. Detection of a germline predisposition has **therapeutic implications** in both the short and long term, such as access to targeted therapy or planning of interventions for the primary cancer diagnosis. In addition, **long-term monitoring** can be **targeted to the specific condition** for early detection or intervention in case of new cancer or symptoms from other organ systems as seen in some hereditary cancer syndromes. For example: Detection of a genetic predisposition had a **clinical effect in 92% in the form of individualised treatment and follow-up in 128 Danish children with brain cancer** and helped clarify any syndromic manifestations beyond the cancer diagnosis[12].

- The finding of a germline predisposition **extends beyond the individual patient** as it enables reproductive options and **genetic testing of family members**, including **identification of relatives at risk** who need follow-up for cancer risk, as well as **genetic clearance** of relatives who consequently do not need follow-up. The possibility of genetic testing in relatives is highlighted in cases such as hereditary haematological cancer, where the use of a bone marrow donor within the family is considered.

- The literature applies varying descriptions of **diagnostic yield**, depending on whether it involves somatic or germline analysis. For example: Three large studies of patients with cancer **generally found a high prevalence (typically 20-100%) of targetable somatic variants** potentially available for targeted therapy[1-3]. Two studies of children with cancer found a germline predisposition in 5-10%[12,13], while the prevalence of a germline predisposition was a few percent to 10% in adults with ovarian, breast, colon, uterine or pancreatic cancer, or haematological cancer[2,11]. Diagnostic yield varied depending on the specific population and method, making comparison across patient groups difficult. However, there is an overall **tendency for a higher diagnostic yield from comprehensive genomic testing, for instance through whole genome sequencing**, than from targeted sequencing, and the diagnostic yield is described as **increasing over time**, probably related to the identification of new targets and new treatment options.

- Across patient groups, the literature describes that the complex genetic landscape of cancer can present **diagnostic challenges**, requiring specialised multidisciplinary collaboration. Knowledge of sequencing methods is essential as technical limitations (e.g. in relation to gene panels or exome sequencing) can cause genetic diagnoses to be missed. Whole genome sequencing offers a comprehensive genomic analysis, but is more expensive and requires complex data analysis. Other limitations include heterogeneous study populations and designs, inconsistent reporting of results and few randomised controlled clinical trials, making it **difficult to compare the clinical effect of targeted therapy**, for instance. In general, the literature mentions a **need for further studies on the clinical effect of genomic diagnostics in cancer** with standardised reporting of results, which requires resources.

- 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, and there are many similarities in the use of whole genome sequencing between these three countries and Denmark. 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**
Haematological cancer	Large overlap
Childhood and adolescent cancer	Almost full overlap
Young adults with cancer and hereditary cancer in adults	Almost full overlap
Disseminated and incurable cancer	Almost 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 experiences with the use of whole genome sequencing in comparable countries for the four cancer patient groups 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.

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 interviews 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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Danish National Genome Center
Ørestads Boulevard 5, Bygning 208
2300 KBH S
Email: kontakt@ngc.dk
Phone: +45 2497 1765
CVR-no: 39851490
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www.ngc.dk