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Whole-exome sequencing in clinical genetics

A health economic evaluation

May 2017

A health economic evaluation

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The budget impact and cost-effectiveness of introducing whole-exome sequencing-based virtual gene panel tests into routine clinical genetics

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Executive summary

Introduction

Harnessing academic and clinical expertise within King's Health Partners (KHP), the KHP Biomedical Diagnostic Hub is working to establish the routine clinical use of next generation sequencing (NGS) technology across the NHS in order to enhance diagnostic and treatment pathways for patients with both rare and common genetic disorders.

Research question

Does the use of exome sequencing for diagnostic testing in constitutional genetics across a range of clinical scenarios and genetic disorders represent a cost-effective use of NHS resources in patients where diagnosis is currently difficult, prohibitively expensive and unavailable in the required time scale or would require invasive procedures?

The study

The study comprised 96 patients selected from a service pilot (2014-2016) for their complex clinical presentations, which were assessed as having a high probability of being an inherited disease. Two scenarios were presented:

- The exome sequencing-based virtual gene panel test is offered in addition to the genetic tests already conducted
- The exome sequencing-based virtual gene panel test is presented as the 'near' first-line test (in addition to any standard reflex first-line tests such as array CGH for developmental delay for example)

Summary

The cost of exome-sequencing based tests (and indeed other genetic tests) accounts for a significant portion of the overall budget required to attempt to establish a diagnosis in these 96 patients. The usual testing strategy will always be the cheapest option (where exome sequencing is not used) except if in scenario 2 the cost of the genetic tests conducted and the clinical workload could be reduced in these patients.

If the cost of the exome sequencing test can bring down the cost of genetic testing for these patients by £943 then the budget required to undertake the exome sequencing test as a near first-line test would be slightly cheaper (£171,593 vs £171,899) in these patients than the current usual testing pathway, with the benefit of potentially increasing the diagnostic yield (by 42.7%).

Conclusions

Ongoing work should focus on trying to reduce the cost of the exome sequencing test (and potentially other baseline tests conducted in addition to exome sequencing) and to investigate the assumption that clinical work up can be reduced if a positive genetic diagnosis is achieved through using such testing as a near first-line test earlier in the patient's diagnostic journey. The experience and results of the service pilot and this economic evaluation provided the basis for the implementation of the new NHS diagnostic exome sequencing service by KHP in 2016.

Introduction

Harnessing academic and clinical expertise within King's Health Partners (KHP), the KHP Biomedical Diagnostic Hub is working to establish the routine clinical use of next generation sequencing (NGS) technology across the NHS in order to enhance diagnostic and treatment pathways for patients with both rare and common genetic disorders.

The Hub developed a pilot project to validate and implement NGS technologies for diagnostic use in constitutional genetics using a list of clinical scenarios and genetic disorders where diagnosis is currently difficult, prohibitively expensive, or requires invasive procedures and would therefore benefit from using the NGS genotyping approach. The NGS approach used in this setting is whole exome sequencing, using the Illumina MiSeq and NextSeq instruments, with a bioinformatics-led analysis pipeline used to interrogate 'virtual disease gene panels' which can be routinely updated and adapted with clinician and clinical scientist input. This report outlines and reports the findings of the health economic evaluation of the pilot project.

Background

Establishing a definitive diagnosis for a patient presenting to the clinical genetics service with a complex condition can entail a lengthy and expensive series of clinical, genetic and often invasive tests. Investigation at the macro-level to investigate large structural abnormalities has traditionally used either karyotyping or more recently microarray comparative genomic hybridisation (arrayCGH). Alternatively 'micro-level' investigation is undertaken using fluorescent Sanger sequencing, widely regarded as the gold standard for accurate sequencing, to identify point mutations within genes. However, both of these investigation techniques have their limitations including relative high cost and low speed in the case of Sanger sequencing. These limitations restrict their application to situations where a complex clinical phenotype leads the clinical geneticist to suspect either the involvement of large known disease genes, such as Nebulin or Titin genes with 183 and 363 exons, respectively, or the investigation of heterogeneous disorders that involve multiple genes such as Long QT syndrome with 12 genes[1].

The advent of NGS with its ability to perform massively parallel sequencing allows many targets to be analysed simultaneously and makes possible the investigation of multiple genes and / or large genes for clinical genetics diagnostic testing. The use of NGS-based targeted gene panels, where multiple pre-specified genes known to be involved with the disease phenotype of interest are co-located on a single panel assay to allow a 'single test' of all these genes together, are being translated into routine clinical genetics service use. However, setting up numerous panels can become impractical as it can be expensive to set-up, optimise and validate individual disease genetic test panels and then also to keep their gene content updated based on the developing evidence-base.

Whole genome and whole exome sequencing assay platforms are now starting to offer alternative means for a clinical genetics laboratory to provide the latest genetic diagnostic tests. This can be through either interrogation of the entire genome or exome sequence – although the increased amount of information is often difficult to interpret and the cost is still high – or by limiting the scope of the analysis through the use of 'virtual gene-panels' where the number of genes interrogated can be adjusted without impacting on the test assay itself which brings down the analytical complexity. This can allow a single laboratory to set-up multiple virtual gene-panels from a single optimised and validated exome or genome sequencing assay. Need *et al.* have shown in a limited 12 patient pilot study that using whole-exome sequencing in a clinical setting can improve the diagnostic yield[2]. However, despite a relatively low per base-pair read cost, the high set-up costs and investment required for the clinical scientists and bioinformatics capability needed to develop, validate and help interrogate the vast data produced presents challenging implementation issues.

Using exome sequencing does increase costs – although not by as much as whole genome sequencing. In its favour, exome sequencing can enable improved health outcomes through the earlier confirmation of disease diagnosis, a more accurate disease prognosis and potentially a better prediction of therapeutic response by:

- Establishing a clinical diagnosis in a greater proportion of patients
- Explaining phenotypic abnormality of unknown aetiology
- Enabling more appropriate and tailored patient management and timely initiation of treatment
- Enabling patients to benefit from existing and emerging treatment trials
- Allowing accurate genetic counselling of family members
- Enabling carrier testing of at risk relatives
- Offering the option of accurate prenatal or pre-implantation diagnosis
- Enabling predictive testing for late onset disorders

The objective of this study is to answer the following decision problem:

> Does the use of exome sequencing for diagnostic testing in constitutional genetics across a range of clinical scenarios and genetic disorders represent a cost-effective use of NHS resources in patients where diagnosis is currently difficult, prohibitively expensive and unavailable in the required time scale or would require invasive procedures?

Methods

Participants

Ninety-six patients were selected based on their complex clinical presentations which had been assessed as having a high probability of being an inherited disease. In addition, existing genetic diagnostic testing of these patients had failed to determine a genetic basis for the clinical diagnosis. These patients are likely to be representative of the types of patients for whom a whole exome sequencing-based virtual gene-panel test could provide the greatest benefits as a much earlier 'near' first-line genetic diagnostic test. The use of exome sequencing-based virtual panels for such patients would be brought forward in the diagnostic testing strategy rather than exhausting all existing available tests first and then moving to exome sequencing.

All these patients had been referred to the regional clinical genetics service at Guy's and St Thomas' NHS Foundation Trust (GSTT) and are representative of patients seen by the service as part of their regional clinical genetics service. GSTT provides the South East Thames Regional Genetics Service for a population of over five million people and also leads the South London NHS Genomic Medicine Centre for the 100,000 Genomes Project.

The 96 patients were selected on the basis that they are likely to be representative of the types of patients for whom a whole exome sequencing-based virtual gene-panel test could provide the greatest benefits as a much earlier 'near' first-line genetic diagnostic test.

In this analysis, it was only necessary to present anonymised data in an aggregated fashion and therefore no patients were identifiable. In accordance with GSTT research governance policies, research ethics approval was not required for this analysis of the pilot.

Study design

A cost-effectiveness analysis was undertaken. This involved a comparison of two intervention arms with a common unit outcome (diagnostic yield). The costs and outcomes were calculated for the two interventions and then the differences in the costs and the differences in the outcomes were calculated so that a ratio of these differences could be presented in the form of an incremental cost-per-outcome. This analysis will use the limited perspective of the diagnostic clinical genetics service which is provided and funded by the NHS.

It was decided not to discount either outcomes or costs because it is assumed that all patients could receive their test results within a single year time-frame. The expected general turn-around time (from sample collection to diagnostic test result) for the exome sequencing test is 168 days. Costs have been reported in UK £s for the year (2015). No power calculation was conducted to determine sample size as this was a pilot project and also because the intention was to estimate the cost and effect differences and using this to undertake an early assessment of whether the use of exome sequencing is cost-effective rather than testing a particular hypothesis concerning cost-effectiveness[3].

Study conditions

Evaluated intervention

The evaluated intervention is the intervention arm in which whole exome sequencing testing is undertaken. This arm includes the genetic testing conducted in addition to the clinical appointments attended in order to construct the genetic testing diagnostic pathway for these patients. Two scenarios have been presented in the following analysis.

- The exome sequencing-based virtual gene panel test is offered in addition to the genetic tests already conducted
- The exome sequencing-based virtual gene panel test is presented as the 'near' first-line test in addition to any standard reflex first-line tests such as array CGH for developmental delay

The second scenario was developed in order to evaluate whether using exome sequencing-based virtual gene panel testing in this potentially more phenotypically complex population could lead to any cost-savings, and if so, under which circumstances.

It is also possible for exome sequencing to reduce the diagnostic odyssey but this was not an outcome captured or used in this study. Following a positive diagnostic exome sequencing test result, a second confirmatory test will be undertaken to confirm the finding as per standard laboratory procedures. The genes included within each of the virtual disease gene sub-panels as tested for these patients are listed in Appendix 1. These virtual disease gene sub-panels are a subset of a larger gene panel assay for a broader disease phenotype category.

The second scenario was developed in order to evaluate whether using exome sequencing-based virtual gene panel testing in this potentially more phenotypically complex population could lead to any cost-savings and if so under which circumstances.

Comparator intervention

The comparator intervention is 'usual testing' and for this study will be taken as all known genetic diagnostic testing undertaken on these patients to date at GSTT. Testing can include existing disease gene panel tests containing any number of genes that do not use clinical exome, whole exome or whole genome-based testing. This arm includes all genetic tests conducted and clinical appointments attended to construct the genetic testing diagnostic pathway in the absence of the exome sequencing test.

Costs

Identification, measurement and valuation of resource use

Costing in economic evaluation is the important aspect of quantifying the different types of resources that are used in each intervention, identifying resource unit costs and then multiplying the quantities by their respective unit costs. This is key for those aspects that differ between the evaluated and comparator arms. Identical aspects across the two interventions can be ignored but only if they are known to be identical. The assumption was made that the market price for the resources used in the evaluated and comparator arms are a reasonable approximation of the actual opportunity cost.

The cost of staff (administrators and clinical staff) was obtained from the NHS Agenda for Change (2015) and the Personal Social Services Research Unit reference costs for 2014/2015. We used the mid-point of each grade and included national insurance, superannuation and overhead costs where not already included. These staff costs were used to calculate the cost of the multidisciplinary team meeting (review meeting) and also the additional clinical selection discussion meeting in the exome sequencing test pathway.

The result review meeting consisted of three clinical geneticists and two clinical scientists presenting the clinical phenotype of a patient, the test requested and the result followed by a discussion of the implications of the test result with a consensus being agreed on future action if any additional work-up is required. On average a patient was discussed in these meetings for 9.1 minutes (based on attendance at two meetings where nine patients were discussed and ranged in time from 3 minutes to 12 minutes).

The clinical selection discussion meeting was estimated to be on average five minutes of brief discussion between one clinical geneticist and one clinical scientist.

The exome sequencing test cost covers all costs to include reagents, consumables, overheads and bioinformatics analysis (including confirmatory testing) to result in a report which the clinical genetics team at GSTT receive and action. All other genetic tests required either as additional tests or as standard first-line tests within the scenario 2 test strategy were identified from the UKGTN website. All cost data collected are reported in Table 1.

Table 1: Estimated resource, test unit costs and assumptions (price year 2015)

Click me

Resource	Consultant clinical geneticist inc. London weight	Clinical Scientist inc. London weight	Array CGH test
Unit cost	£2.61	£0.83	£250
Unit description	Medical consultant unit cost per hour including London weight of client contact time divided by 60 for a cost per minute.	Agenda for Change band 7 mid-point recalculated using CCEMG-EPPI-Centre Cost Convertor to bring in line with 2015 prices cost per hour calculated using same assumptions as Curtis (2015) and then multiplying normal wage by London multipliers at 1.14 and 1.55	NHS internal test price at GSTT clinical genetics service
Source	Page 235 in Curtis (2015)	AfC 2014	GSTT
Assumptions			Unit price includes the cost of all test procedures, reagents, staff costs, overheads and bioinformatics analysis required to result in the report that the clinical consultant receives.

It was first necessary to confirm the steps of the two intervention arms as reported above. Based on discussions with key staff from the GSTT laboratory and clinical genetics service a testing pathway was constructed. A laboratory visit was also made in order to understand the various procedures taking place. Following discussion, additional observations made on the laboratory visit, and a presentation to key members of the GSTT laboratory and clinical genetics service, the steps presented in Figure 1a and Figure 1b were confirmed as accurate and formed the basis for the decision tree used for the cost-effectiveness analysis.

Cost data requirements for diagnostic genetic testing at GSTT for the 96 patients were discussed, confirmed and then extracted and provided by the GSTT Regional Genetics Service as were the clinical units of any clinical service appointment and work-up. Where provided, these were actual costs incurred by the clinical genetics service. These data were collated for each patient in an anonymised format in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA).

Clinical units are the activity measure used at GSTT for calculating the clinical workload associated with clinical workup and clinical genetics appointments. For example, a face-to-face appointment including one patient is 4 clinical units worth of activity. Additional family members receiving advice at the same appointment would accrue an additional clinical unit of activity. A telephone appointment that replaces a face-to-face appointment incurs 3 clinical units. A review and summary report with screening advice from the hereditary bowel and cancer MDT accrues 3 clinical units. Clinical units were costed at £80 per unit.

Outcomes

The main outcome of interest for this study is the number of positive diagnoses produced by an intervention (diagnostic yield) so that an incremental cost-per-diagnosis can be calculated for the cost-effectiveness analysis.

- The number of positive diagnoses made was calculated from the patient data and was provided in an anonymised form by the laboratory following confirmatory testing
- The diagnostic yield was calculated as the number of positive diagnoses divided by the total number of patients tested

In this study a positive diagnosis is defined as a patient in whom a variant has been detected that is believed to be causal in relation to the clinical and phenotypic symptoms presented by the patient. The evaluation of variant pathogenicity and reporting was in accordance with current best practice based on the practice guidelines developed by the Association for Clinical Genetic Science[4].

For the purposes of this analysis, in calculating the diagnostic yield patients with either unresolved results or variants of unknown significance were grouped with the patients with no diagnosis. It is possible that as the clinical significance of new evidence for variants accumulates, a variant of unclear significance today may become a variant with a known pathological or benign impact in the future. Whilst it may be that any additional resources to routinely check variants of unknown significance against a database may be relatively minimal to the cost of undertaking the original sequencing work, we have excluded this potential change in future laboratory practice and the cost associated with a re-analysis as this was outside the scope of this work.

Figure 1a: Usual genetic diagnostic testing pathway (simplified)

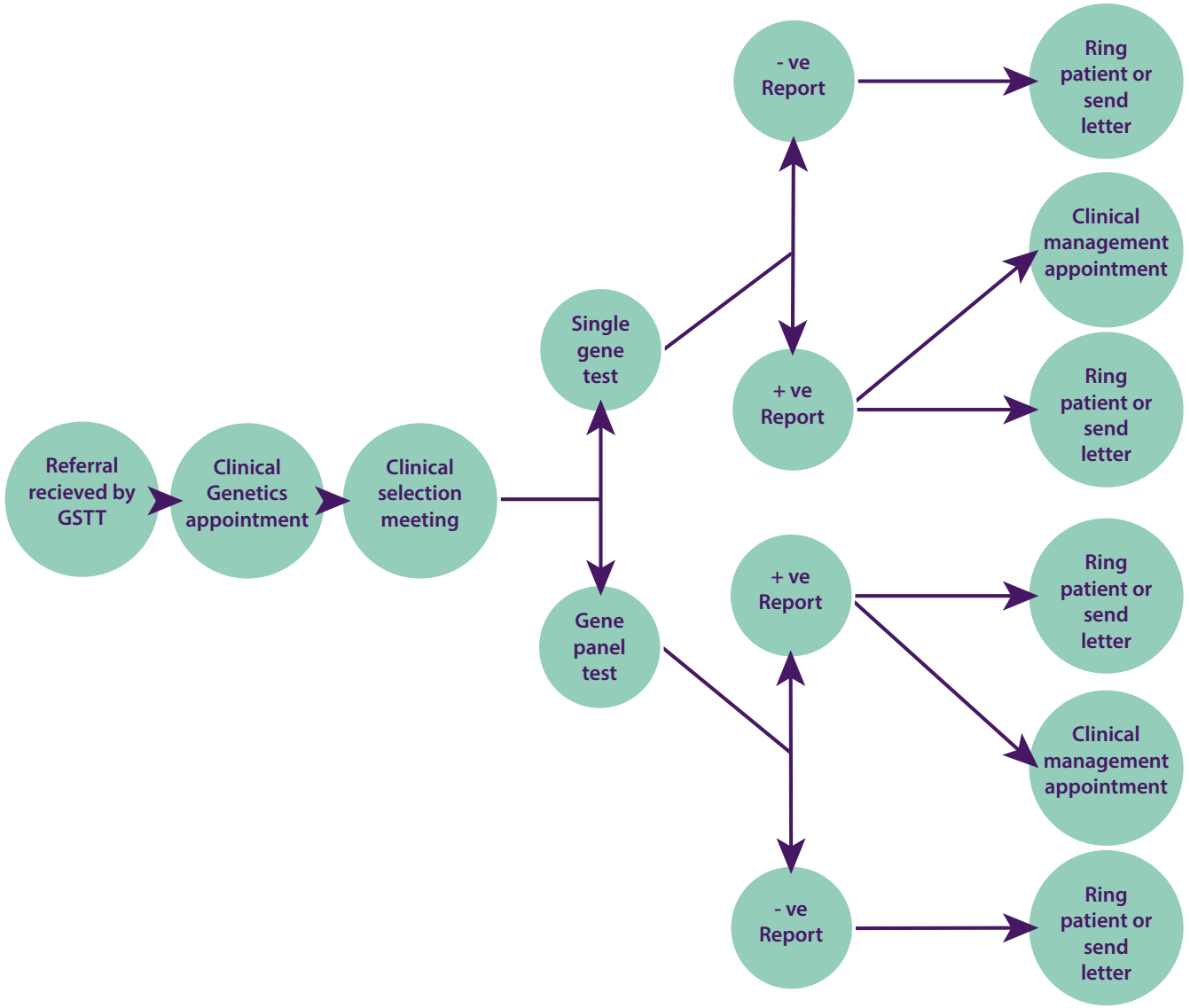
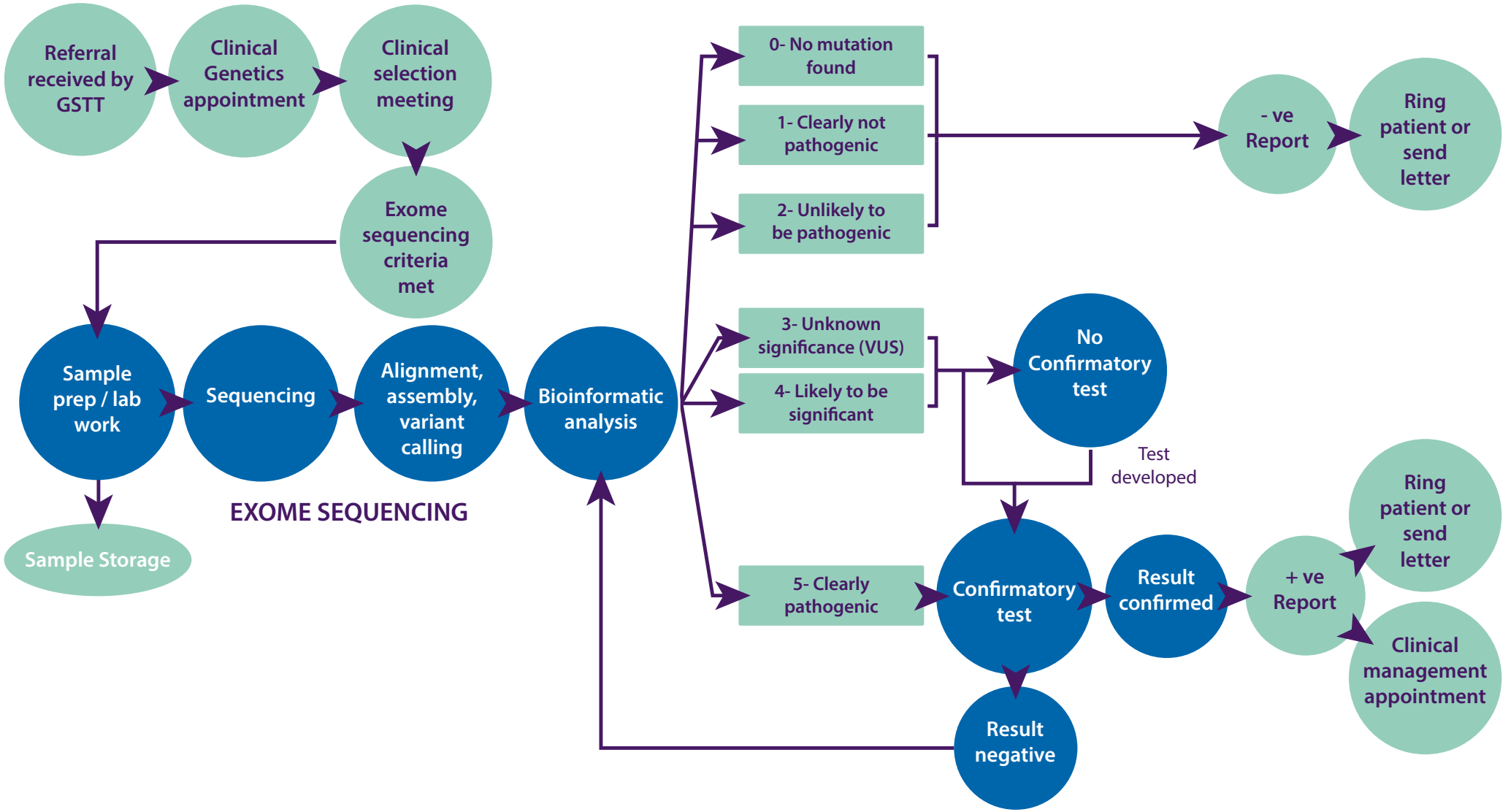


Figure 1b: Exome sequencing diagnostic testing pathway



To fully capture the true value of diagnostic genetic testing, improvements in both the evidence-base and the methods for incorporating the non-health outcomes and patient preferences into an economic evaluation are required to inform better value-based reimbursements[5]. However, the capture and inclusion of 'non-health' outcomes was outside the scope of this work.

Diagnostic outcome data were collated for the 96 patients and provided by the GSTT service. Diagnostic yield was calculated from these data.

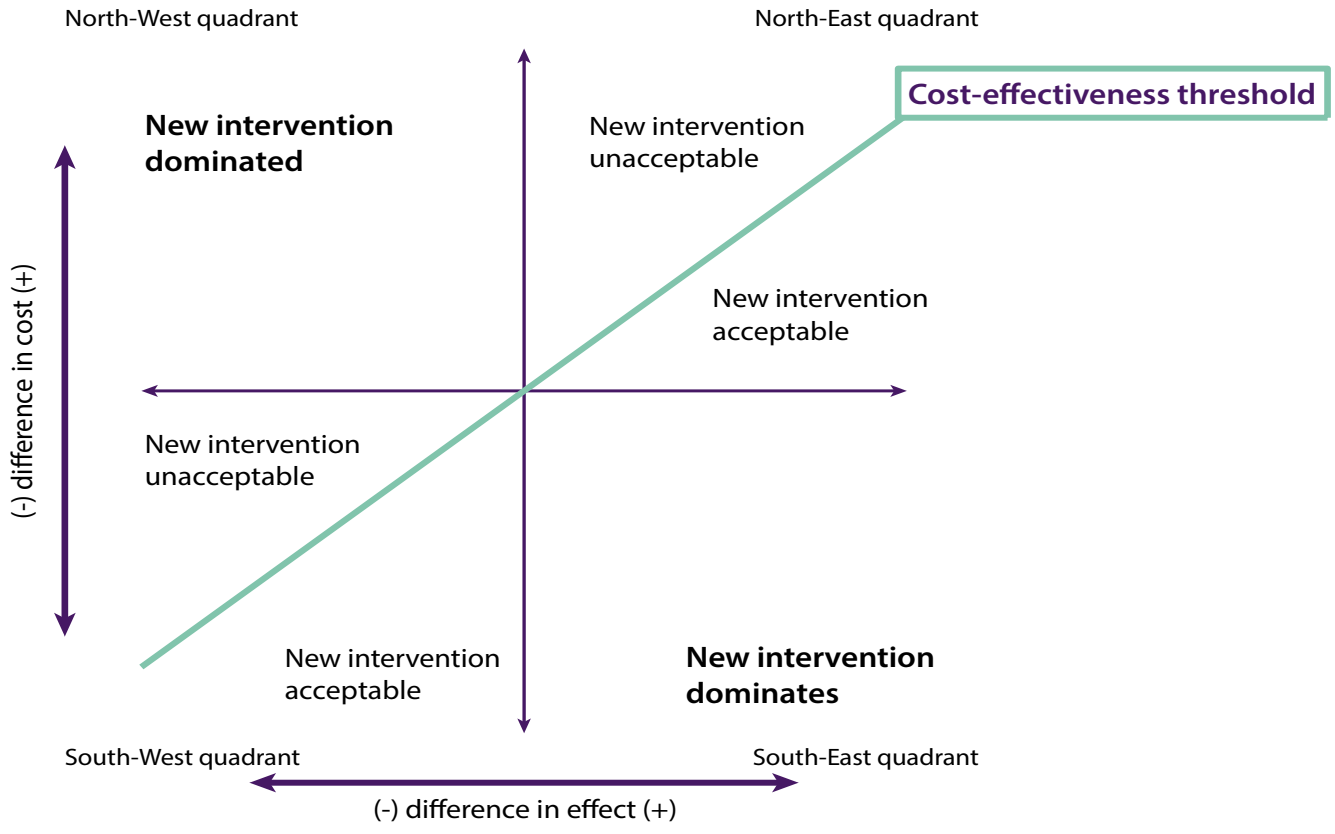
Cost-effectiveness analysis

Cost-effectiveness analysis is a full form of economic evaluation where both the costs and consequences of an intervention are evaluated together. The cost-effectiveness of the two interventions is calculated as the incremental cost-effectiveness ratio (ICER) which is defined as the difference between the costs of the two interventions divided by the difference in the outcomes (number of diagnoses) of the two interventions.

If a new intervention is shown to cost less and is more effective than the current intervention it is called dominant and represents a cost-effective use of resources. This can be represented on a cost-effectiveness plane (see Figure 2) as an ICER point estimate being located in the South-East quadrant.

Conversely, if the new intervention is shown to cost more and is less effective than the current intervention it is dominated and should not be implemented. This can be represented on the cost-effectiveness plane in Figure 2 as an ICER point in the North-West quadrant. ICER point estimates in the other two quadrants require a cost-effectiveness threshold to which the estimate must be compared in order to determine whether it is 'cost effective'. If the health system is willing to pay the trade-off between cost and benefit under this threshold then the new intervention is acceptable and should be implemented. If above the threshold then unless other factors take precedence (such as equity issues) then the new intervention is not acceptable and should not be implemented.

Figure 2: The cost-effectiveness plane and its use



The ICER compares the cost and effect of the two interventions using the formula ($Cost_B$ – $Cost_A$) / ($Effect_B$ – $Effect_A$) where $Cost_A$ is the mean cost of the exome sequencing test pathway, $Cost_B$ is the mean cost of the usual testing pathway, $Effect_A$ is the diagnostic yield of the exome sequencing test pathway, and $Effect_B$ is the diagnostic yield of the usual testing pathway. All data analyses were conducted in Microsoft Excel 2010.

Budget impact

In addition to the cost-effectiveness analysis we also undertook a budget impact analysis. A budget impact analysis is a tool to predict the potential financial impact of adopting a new technology into a healthcare system with finite resources[6]. This was done in order to understand the resource implications of utilising exome sequencing as a diagnostic genetic test.

Using the testing pathways as defined for the cost-effectiveness analysis, the overall costs for both pathways were calculated. Costs are reported in 2015 UK pounds (£) and presented from the perspective of the clinical genetics service encompassing the referral of a patient for diagnostic genetic testing through to the result of either the existing usual testing pathway or the use of the exome sequencing test. Average testing pathway costs per patient are presented for the two pathways along with the total budget required to test these 96 patients.

Key assumptions

As part of a modelling framework, it is necessary to make a number of assumptions in order to enable such an analysis to be carried out. These are described below:

- The analysis was limited to the diagnostic testing pathway within clinical genetics (which would run from referral through to a test result and include the test costs and also the clinical appointments and work-up costs incurred by the genetics service).
- The laboratory charge for full exome sequencing was set at a price of £1300. This charge is assumed to cover all costs and includes reagents, consumables, overheads, human resources, associated bioinformatics analysis for the virtual disease gene sub-panel test (whether in-house development of bespoke software or licence fees to external agencies for software use) and confirmatory testing for any positive or ambiguous results all of which then lead to a result and a diagnostic report which the clinical genetics team at GSTT can action. Furthermore, it is assumed that the price includes training of laboratory staff, equipment purchase / lease and implementation (running) costs.

Sensitivity analyses

Sensitivity analyses allow insight into which assumptions or restrictions on the data included are important to the overall result and conclusion being drawn from the analysis of the data. Given the early nature of the cost-effectiveness analysis being conducted on this pilot dataset a pragmatic approach to conducting one-way sensitivity analyses was used. The following parameters were changed in order to explore their impact on both the cost-effectiveness and the overall budget required to test these 96 patients so that some broader conclusions can be drawn:

- The cost of the exome sequencing test was reduced in increments of £200
- The cost of the clinical work-up was varied (+/- by increments of 25% up to 75%)
- The cost of the multidisciplinary team meeting (review meeting) was increased (by 100%)

Results

Ninety-six patients were included in this cost-effectiveness study. The basic demographic characteristics of these 96 patients were 51 male (53.1%), 45 female (46.9%), with an average age at the end of 2016 of 24.5 years old, a median age of 16 years old and ranging from 3 years old to 82 years old.

The clinical presentation of the 96 patients (panel category tested) along with the whole exome sequencing-based virtual disease gene sub-panel test chosen for each patient is shown in Table 2 with details on which genes were included listed in Appendix 1.

Over half of patients had a clinical presentation suitable to being tested for with a sub-panel of the Dysmorphology virtual gene panel (40 patients - 21 female and 19 male) or the Skeletal virtual gene panel (18 patients - 10 female and 8 male). In summary, 10 patients were tested for the Cardiomyopathy virtual gene panel (6 male and 4 female), 10 patients for the Connective Tissue Disorders (CTD) virtual gene panel (8 male and 2 female), 6 patients for a sub-panel of the Renal virtual gene panel (4 male and 2 female), 5 patients for the Endocrine virtual gene panel (4 male and 1 female), 3 patients for the Ophthalmology virtual gene panel (all female), 2 patients for the Neurology virtual gene panel (1 male and 1 female), and 1 patient each for the Cancer and Epilepsy virtual gene panels (1 male and 1 female, respectively).

Costs

Comparator intervention

For the 'usual testing' arm, the genetic tests already conducted at GSTT that have thus far failed to provide a positive diagnosis in this group of patients were combined with the clinical genetics appointments attended in order to produce a patient genetic testing diagnostic pathway.

- The mean cost for genetic testing alone in this group of 96 patients was £831 (ranging from £0 to £4,045)
- The average number genetic tests undertaken at GSTT was 3 (ranging from 0 to 9)
- The average number of clinical appointments attended and clinical units incurred for this group of 96 patients were 3 (ranging from 1 to 13) and 14 (ranging from 3 to 60) respectively
- The mean cost of this clinical work-up was £960 (ranging from £0 to £4,800)
- The mean cost of the genetic testing diagnostic pathway (consisting of both genetic testing and clinical appointments) was £1,791 (ranging from £0 to £8,466)

Evaluated intervention

In scenario 1, patients were offered exome sequencing in addition to the genetic tests already conducted.

- This scenario had a mean cost for genetic testing alone of £2,185 (ranging from £1,317 to £5,362). This was on average £1,354 more expensive than the comparator intervention (95% CIs: £984 to £1,725) which was statistically significant ($p<0.000001$)
- The clinical work-up was assumed to remain the same as in the usual testing arm
- The mean cost of the exome sequencing in addition to usual testing scenario pathway (both genetic testing and clinical appointments) for these 96 patients was £3,145 (ranging from £1,317 to £9,783)

Table 2: Clinical presentation and whole exome sequencing panel test for each of the 96 patients

Dysmorphology
Skeletal
Cardiomyopathy
CTD
Renal
Endocrine
Ophthalmology
Neurology
Epilepsy
Cancer

Panel category tested	Sex	Clinical sub-panel tested
Dysmorphology	Female	Ochoa
Dysmorphology	Male	Cohen syndrome
Dysmorphology	Male	Noonan syndrome
Dysmorphology	Female	Steiner syndrome
Dysmorphology	Female	Coffin Siris
Dysmorphology	Female	Coffin Siris/ Floating Harbor/ Rubinstein Taybi.
Dysmorphology	Male	Cerebellar atrophy with query about Goldberg-Shprintzen
Dysmorphology	Female	Coffin Siris
Dysmorphology	Female	Smith-Magenis
Dysmorphology	Male	Treacher Collins
Dysmorphology	Female	Holoprosencephaly
Dysmorphology	Male	Rubinstein-Taybi
Dysmorphology	Female	Arthrogryposis
Dysmorphology	Male	Mowat-Wilson
Dysmorphology	Female	Albright
Dysmorphology	Female	Steiner
Dysmorphology	Male	Kabuki
Dysmorphology	Female	Beals syndrome (*FBN2*)
Dysmorphology	Male	Sotos-like
Dysmorphology	Female	*RECQL4*
Dysmorphology	Male	Noonan (*PTPN11* N)
Dysmorphology	Male	Floating-Harbor syndrome
Dysmorphology	Female	SLO
Dysmorphology	Male	Wolfram
Dysmorphology	Female	*OFD1*
Dysmorphology	Male	Van der Woude syndrome
Dysmorphology	Male	Craniometaphyseal dysplasia
Dysmorphology	Female	Rett-like
Dysmorphology	Male	Seip syndrome
Dysmorphology	Female	IFAP-like
Dysmorphology	Male	Kabuki/Aarskog
Dysmorphology	Male	RAS-opathy
Dysmorphology	Male	Gordon syndrome
Dysmorphology	Female	Hypodontia
Dysmorphology	Female	Hypodontia
Dysmorphology	Female	Ectodermal dysplasia
Dysmorphology	Male	KBG
Dysmorphology	Male	Kabuki
Dysmorphology	Female	Bloom syndrome
Dysmorphology	Female	Kleefstra

For scenario 2, a modelling exercise was undertaken where the patients would be offered the exome sequencing based test as a near first-line test rather than as the second-line test as per scenario 1.

- The estimated mean cost for the exome sequencing test was £1,354 (ranging from £1,317 to £1,393)
- The estimated mean cost of baseline testing in addition to the exome sequencing was £416 (ranging from £0 to £1,000)
- The estimated mean cost of total genetic testing was £1,770 (ranging from £1,317 to £2,393). This was on average £939 more expensive than the comparator intervention (95% CIs: £619 to £1,260) which was statistically significant ($p<0.0000001$). Again the clinical appointments and work-up were assumed to remain the same as in the usual testing arm
- The estimated mean cost of the exome sequencing as a near first-line test scenario pathway for these 96 patients (both genetic testing and clinical appointments) was £2,730 (ranging from £1,317 to £7,117)

Outcomes

Comparator intervention

The main outcome for this study was the number of positive diagnoses produced by each diagnostic testing pathway so that a cost-per-diagnosis can be calculated. The 96 patients were selected on the basis that they represented a group where the use of exome sequencing was likely to be beneficial because they had not yet received a positive genetic diagnostic result from the genetic testing already conducted. The diagnostic yield was therefore 0%.

Evaluated intervention

The exome sequencing results for these 96 patients are shown in Figure 3. Of the 96 patients tested, 41 (42.7% diagnostic yield) had received a positive genetic diagnosis, where a positive diagnosis is defined as a patient in whom a variant has been detected that is believed to be causal in relation to the clinical and phenotypic symptoms presented by that patient. Forty-nine patients did not receive a positive genetic diagnosis (51%) and the remaining 6 patients were cases where the results did not fully explain the phenotype. For the purposes of this analysis, the 6 unresolved patients* were assumed to be negative and were grouped with the 49 patients that did not receive a positive genetic diagnosis. The results broken down by genetic test panel are presented in Table 3. A greater than 50% diagnostic yield was observed in three of the virtual disease gene sub-panels included within this pilot (Renal, Endocrine, and Skeletal).

The Dysmorphology, Cardiomyopathy, and CTD virtual disease gene sub-panels also showed high diagnostic yields of 42.5%, 40%, and 30% respectively. These are all patients that had failed to achieve a positive genetic diagnosis from existing testing strategies. The four remaining panels (Ophthalmology, Neurology, Epilepsy, and Cancer) failed to identify any positive genetic diagnosis, although this could also be due to the small numbers involved – $n<5$ for each of the four panels).

*At the time of writing this report these six patients remained unresolved. Four of the six patients produced results that were consistent with their clinical phenotype but did not fully explain the phenotype so were being investigated further. The two remaining patients had one variant detected for an expected recessive disorder (where two variants are required) and were being further investigated.

Figure 3: Exome sequencing results showing the diagnostic yield

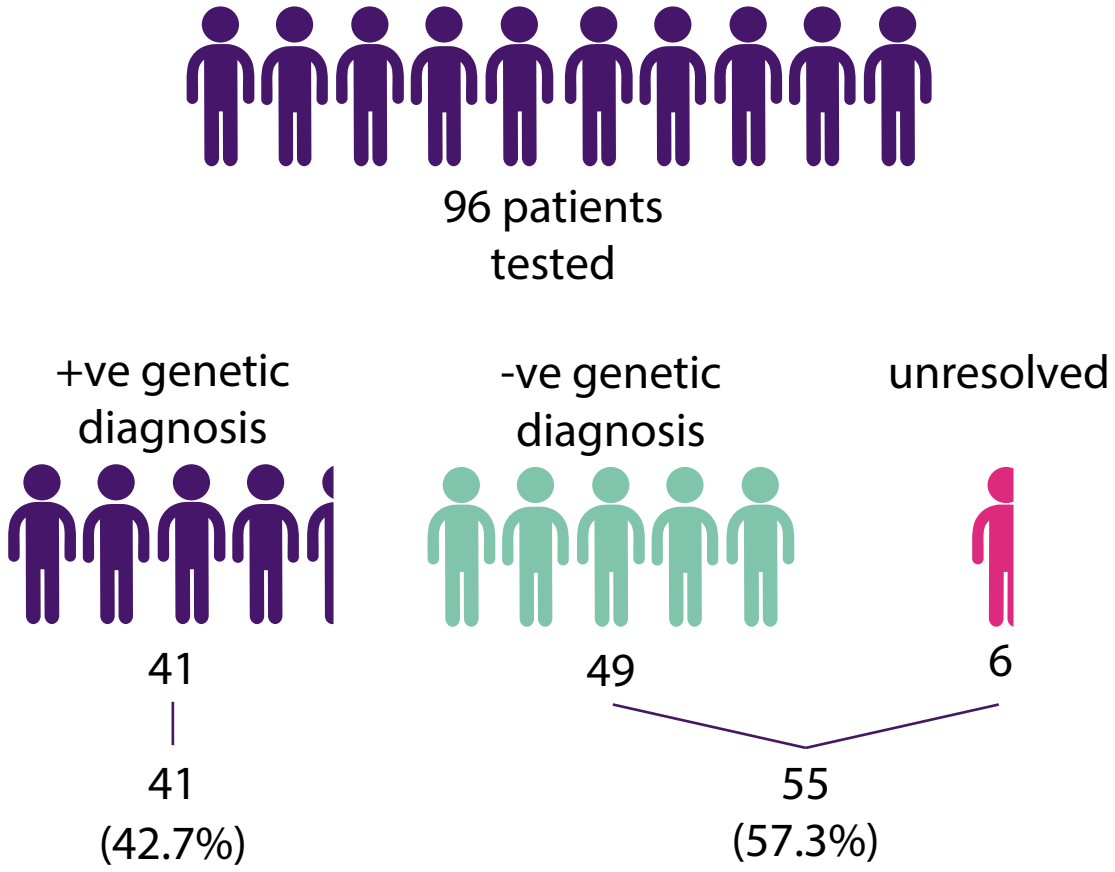


Table 3: Diagnostic test results and yield broken down by type of panel for the cohort of 96 patients

Panel category tested	Number of patients tested	Number of positive genetic diagnosis	Diagnostic yield
Dysmorphology	40	17	42.5%
Skeletal	18	10	55.6%
Cardiomyopathy	10	4	40%
CTD	10	3	30%
Renal	6	4	66.6%
Endocrine	5	3	60%
Ophthalmology	3	0	0%
Neurology	2	0	0%
Epilepsy	1	0	0%
Cancer	1	0	0%
Total	96	41	42.7%

Cost-effectiveness analysis

When a new intervention is shown to be more effective but costs more than the existing intervention, it cannot dominate the existing intervention, i.e. be cheaper and better – an easy adoption situation. As it is more expensive, it is likely to cost more to implement but can still represent a cost-effective use of resources.

For scenario 1 where patients would be offered exome sequencing in addition to the genetic tests already conducted in the usual testing arm, the incremental cost-effectiveness ratio (ICER) was calculated to be £3,171. This corresponds to an incremental cost per additional positive genetic diagnosis of £3,171 when compared to the usual testing approach in these 96 patients. This was calculated by dividing the incremental cost of the two testing strategies (£135,400) by the incremental diagnostic yield of the two interventions (42.7 diagnoses per 100 patients tested).

For scenario 2, where patients would be offered the exome sequencing test as a near first-line test rather than as a second line test in addition to the usual genetic tests, the ICER was calculated to be £2,201. This corresponds to an incremental cost per additional genetic diagnosis of £2,201 when compared to the usual testing approach in these 96 patients. This was again calculated by dividing the incremental cost of the two testing strategies (£94,000) by the incremental diagnostic yield of the two strategies (42.7 diagnoses per 100 patients tested).

Whilst the willingness to pay for a QALY in the NHS is known (£20,000 to £30,000) there is no universally acknowledged willingness to pay threshold for a diagnosis. This makes interpreting these results more difficult. The budget impact analysis was undertaken so that the financial resource implications of implementing exome sequencing can be better understood.

Sensitivity analyses

The results of the sensitivity analysis are presented in Table 4. They show that changing the cost of the exome sequencing test has a large impact on the ICER. In addition its shows how the ICER reduces for scenarios 1 and 2, if the cost of the exome sequencing test is reduced in increments of £200. It can be seen that scenario 2 would dominate usual testing if the cost of genetic testing could be reduced by £1,000.

Assuming that receiving a positive genetic diagnosis more quickly would reduce the number of clinical appointments and also the associated clinical work-up, the impact of reducing the clinical resource cost in those patients with a positive diagnosis was investigated. As can be seen in Table 4, reducing the clinical cost in positive diagnosed patients has a smaller impact than a reduction in the cost of the sequencing test. Table 4 also shows that increasing the cost of the results meeting by 100% has a small impact on the ICER. The diagnostic yield for the usual testing strategy was not increased in a sensitivity analysis as interpretation of any increase in ICER would remain difficult to interpret due to no acknowledged NHS willingness-to-pay threshold for a diagnosis.

Table 4: Sensitivity results for cost-effectiveness analysis of scenarios 1 and 2

Sensitivity analysis	Scenario 1 ICER (£ per additional diagnosis)	Scenario 2 ICER (£ per additional diagnosis)
Baseline results	£3,171	£2,201
Reduce cost of genetic testing by £200	£2,703	£1,732
Reduce cost of genetic testing by £400	£2,235	£1,264
Reduce cost of genetic testing by £600	£1,767	£796
Reduce cost of genetic testing by £800	£1,298	£327
Reduce cost of genetic testing by £1,000	£830	Dominates
Reduce clinical work up by 25%	£2,931	£1,961
Reduce clinical work up by 50%	£2,691	£1,721
Reduce clinical work up by 75%	£2,451	£1,481
Increase cost of MDT by 100%	£3,349	£2,379

Budget impact

For the usual testing pathway, the overall budget and the average per-patient testing pathway cost were £171,899 and £1,791, respectively based on these 96 patients. Of this £171,899 budget, £92,160 is accounted for by the clinical appointments and clinical work-up (53.6%) and £79,739 (46.4%) is accounted for by the genetic testing costs.

For scenario 1, the exome sequencing test pathway in addition to usual testing, the overall budget and the average per-patient testing pathway cost were £301,926 and £3,145, respectively. The overall budget required has increased by £130,027 (75.6%). The increase in budget is largely accounted for by the increase in genetic test costs with £209,767 attributed to testing (69.5%) versus the clinical work up which was kept the same (£92,160), but now constitutes a smaller percentage of the overall budget (31.5%).

For scenario 2, the exome sequencing test pathway as a replacement for usual testing (i.e. exome as a near first-line test), the overall budget and the average per-patient testing pathway cost were £262,122 and £2,730, respectively. The overall budget has increased by £90,223 (52.5%) compared to usual testing with the increase again being largely due to the increased cost of the exome sequencing test with £169,962 of the budget due to genetic testing (64.8%) and the clinical work-up making up the remaining 35.2%.

Sensitivity analyses

The larger budget required for the two scenarios using the exome sequencing test pathway highlights the increased current cost of the exome sequencing test itself. The results of the sensitivity analysis are presented in Table 5.

In summary, if the cost of the exome sequencing test, and any associated baseline tests such as array CGH, can be reduced by £943, then the budget required to undertake the exome sequencing test as a near first-line test would be slightly cheaper (£171,593 vs £171,899) than the current usual testing pathway. An additional benefit is a potential increase in the diagnostic yield of 42.7%. If Sanger sequencing confirmatory testing is removed (as is currently being proposed) then this would further reduce the cost of exome sequencing testing. Furthermore, if the bioinformatics analysis could be further automated then this may also reduce the laboratory cost of testing as this cost was included within the overall exome sequencing test charge.

Again, assuming that receiving a positive genetic diagnosis more quickly will lead to a reduction in the number of clinical appointments required and also the associated clinical work-up, the impact of reducing the clinical resource used for those with a positive genetic diagnosis was investigated. As can be seen in Table 5, reducing the clinical cost in positive genetic diagnosis patients has a smaller impact than a reduction in the cost of the exome sequencing test. Due to the results meeting contributing only a small percentage of the overall cost, increasing the cost of the meeting by 100% has little impact on the overall budget.

> If Sanger sequencing confirmatory testing is removed, as is currently being proposed, then this would further reduce the cost of exome sequencing testing.

In scenario 2, the mean cost of genetic testing for these 96 patients is £1,770. A reduction of £943 (53%) is a significant reduction but can be made up by not only reducing the exome sequencing test cost but also reducing the cost of any other baseline tests that are undertaken, e.g. by not performing array CGH. Furthermore, it would be possible to reduce the budget in scenario 2 by either combining a reduction in clinical work up of 25% and a reduction in genetic test costs of £840 or a reduction in clinical work up of 50% and a £740 reduction in genetic test costs to make scenario 2 potentially cost saving with respect to the overall budget required to test these 96 patients (See Table 5).

Table 5: Sensitivity analysis results for budget impact analysis

Sensitivity analysis	Usual testing	Scenario 1	Scenario 2
Baseline	£171,899	£301,926	£262,122
Reduce cost of genetic testing by £100	£171,899	£292,325	£252,521
Reduce cost of genetic testing by £200	£171,899	£282,725	£242,921
Reduce cost of genetic testing by £400	£171,899	£263,525	£223,721
Reduce cost of genetic testing by £800	£171,899	£225,125	£185,321
Reduce cost of genetic testing by £943	£171,899	£211,397	£171,593
Reduce clinical work up by 25%	£171,899	£292,085	£252,282
Reduce clinical work up by 50%	£171,899	£282,246	£242,442
Reduce clinical work up by 75%	£171,899	£272,406	£232,602
Increase cost of results meeting by 100%	£171,899	£309,222	£269,418
Two-way sensitivity scenario			
Reduce clinical work up by 25%, and reduce cost of genetic testing by £740	£171,899	£211,446	£171,642
Reduce clinical work up by 50%, and reduce cost of genetic testing by £840	£171,899	£211,206	£171,402

Breakdown by panel

In Tables 6a and 6b the summary results for usual testing and scenarios 1 and 2 are presented by genetic test panel for the overall budget, the mean cost per patient testing pathway, the mean cost per positive patient diagnosis and the ICER. As can be seen in the two tables, the ICERs vary across the disease panels in scenario 1 between £2,052 to £4,467 per additional positive genetic diagnosis and in scenario 2, it is between £1,110 to £3,385 per additional positive genetic diagnosis.

Table 6a: Summary results showing budget impact and ICERs comparing usual testing and scenario 1 broken down by panel

	Usual testing		Scenario 1			
Panel category tested	Budget (£)	Average cost per patient (£)	Budget (£)	Average cost per patient (£)	Average cost per positive patient (£)	ICER
Dysmorphology	74,734	1,868	128,868	3,222	7,580	3,184
Neurology	3,340	1,670	6,050	3,025	-	-
CTD	20,957	2,096	34,357	3,436	11,452	4,467
Epilepsy	1,442	1,442	2,760	2,760	-	-
Ophthalmology	6,324	2,108	10,428	3,476	-	-
Renal	10,771	1,795	18,979	3,163	4,745	2,052
Cancer	3,118	3,118	4,436	4,436	-	-
Endocrine	8,764	1,753	15,654	3,131	5,218	2,297
Skeletal	37,527	2,085	61,997	3,444	6,200	2,447
Cardiomyopathy	4,921	492	18,397	1,840	7,580	3,369

Table 6b: Summary results showing budget impact and ICERs comparing usual testing and scenario 2 broken down by panel

	Usual testing		Scenario 2			
Panel category tested	Budget (£)	Average cost per patient (£)	Budget (£)	Average cost per patient (£)	Average cost per positive patient (£)	ICER
Dysmorphology	74,734	1,868	107,414	2,685	6,318	1,922
Neurology	3,340	1,670	5,050	2,525	-	-
CTD	20,957	2,096	31,110	3,111	10,620	3,385
Epilepsy	1,442	1,442	2,047	2,047	-	-
Ophthalmology	6,324	2,108	6,774	2,258	-	-
Renal	10,771	1,795	15,212	2,535	3,803	1,110
Cancer	3,118	3,118	3,617	3,617	-	-
Endocrine	8,764	1,753	13,250	2,650	4,417	1,496
Skeletal	37,527	2,085	60,800	3,378	6,080	2,327
Cardiomyopathy	4,921	492	16,846	1,685	4,212	2,981

Discussion

Summary of findings

In this cost-effectiveness study based on a cohort of 96 patients, the use of whole exome sequencing based testing was compared to existing clinical testing through the use of two testing strategies (Table 7). The existing testing strategy was defined as all known diagnostic testing undertaken on this cohort of 96 patients to date at GSTT.

The two whole exome sequencing strategies used were:

- Scenario 1, exome sequencing test is offered as a second-line test following a negative result of all the existing tests conducted already on these patients
- Scenario 2, the exome sequencing test is presented as a near first-line test, in addition to any baseline tests such as array CGH that would likely be conducted regardless of the availability and use of exome sequencing

The use of exome sequencing produced a diagnostic yield of 42.5% across this mixed-patient group. The diagnostic yield was as high as 66.6% in the renal patient group with six of the ten panels used producing diagnostic yields of 30% and above.

Table 7: Summary results

Test strategy	Total budget	Clinical cost (%)	Testing cost (%)	Mean cost per patient (range)	Mean cost per positive diagnosis	ICER (versus usual testing)
Usual testing	£171,899	53.6%	46.4%	£1,791 (£0 to £8,466)	-	-
Scenario 1	£301,926	31.5%	69.5%	£3,145 (£1,317 to £9,783)	£7,364	£3,171
Scenario 2	£262,122	35.2%	64.8%	£2,730 (£1,317 to £7,117)	£6,393	£2,201

- Sensitivity analyses showed that the largest driver of cost was the cost of the genetic testing, including the cost of the exome sequencing and the associated bioinformatics analysis
- Scenario 1 will always be the most expensive option as the costs of usual testing are incurred before going on to use exome sequencing in those patients in which the genetic tests conducted are negative
- The usual testing strategy, where exome sequencing is not used, will always be the cheapest option except if in scenario 2 the cost of the genetic tests conducted and the clinical workload could be reduced in these patients. For example, if the cost of the genetic testing for these 96 patients could be brought down by £943 in scenario 2 then the overall budget required to test the 96 patients would be slightly cheaper than the actual incurred by the usual testing strategy (£171,593 vs £171,899) with the added benefit of potentially increasing the diagnostic yield by 42.7% across this mixed patient group. In scenario 2, the mean cost of baseline testing conducted in addition to the exome sequencing itself was £416 (ranging from £0 to £1,000). This means that if this was removed and the price of the exome sequencing test could be reduced from £1,300 to £803 then no increase in budget would be required if everything else remains constant. Furthermore, the expectation is that in the future confirmatory Sanger sequencing will no longer be required which will bring the cost of exome sequencing-based testing down further by removing this cost from the laboratory pathway

Limitations

There are several limitations to this evaluation. The health economics analysis focused on a pilot cohort of 96 patients chosen specifically based on their complex clinical presentations and which had been assessed as having a high probability of an inherited disease.

In addition, these patients presented across a range of clinical scenarios where diagnosis is difficult, prohibitively expensive or required invasive procedures and where existing genetic diagnostic testing had thus far failed to determine a genetic basis for the clinical presentation. Whilst these patients are very likely to reflect the actual NHS patients that would receive and benefit from having a whole exome sequencing based test (a particular strength of this work), their use meant that the diagnostic yield for the current testing arm was 0%. Whilst for scenario 1 the increase in diagnostic yield observed is a true reflection of what can be expected if whole exome sequencing-based virtual gene panel testing is applied in patients similar to this, it may be an underestimate in scenario 2 as the true near first-line testing patient population would include all patients that would be expected to be identified with a positive diagnosis by current testing (who were purposely excluded here in this cohort). Furthermore, the diagnostic yield may also change when applied to a much larger cohort of patients depending on the clinical spectrum. However, due to the large current expense in conducting a whole exome sequence it is still very likely that the test will not be routinely offered as a true first-line test and there will remain a triaging process to decide when to offer such a test – something that has already been applied to these patients. However, the per-test exome sequencing costs could be reduced by achieving an economy of scale that maximises patient throughput and creates efficiency savings by utilising the common diagnostic pathway introduced by whole exome sequencing based virtual gene panels.

Whilst for scenario 1 the increase in diagnostic yield observed is a true reflection of what can be expected if whole exome sequencing-based virtual gene panel testing is applied in patients similar to this, it may be an underestimate in scenario 2 as the true near first-line testing patient population would include all patients that would be expected to be identified with a positive diagnosis by current testing.

Access to these patients' data is limited to clinical work-up or diagnostic testing conducted only at GSTT. These patients may have received genetic testing elsewhere within the NHS, information that GSTT do not have access to, but leading to an underestimation of the cost. Therefore the potential increase in cost to undertake whole exome sequencing in these 96 patients may be smaller than presented. Also, given that GSTT is a well-established leading regional genetics service, the patient referrals seen by the service may be more complex than those seen in other parts of the country. When coupled with the expertise and experience GSTT has developed in choosing which disease genes to test in the virtual disease gene sub-panel tests there may well be an impact on the diagnostic yield of using whole exome sequencing tests.

In this evaluation the outcome of interest was limited to the diagnostic test result. The perspective was narrow and included only the costs and outcomes for the diagnostic genetic testing pathway. This was done for pragmatic reasons in order to limit the evaluation to activity and costs within the directorate's budget, as often patient treatment costs are incurred by other specialties as are other test costs. Furthermore, the patient level data requirement would have substantially increased if a wider perspective was sought.

This limitation impacts in several ways on such an analysis. It is possible that receiving a positive genetic diagnosis may result in more appropriate care being delivered for patients with improved health outcomes but this could either result in increased or decreased costs in terms of their future treatment options and can alter the need for further testing. Furthermore, no benefit apart from that for the patient was assigned to receiving a positive genetic diagnosis, such as information for parents and also no disbenefit was assigned to those patients that did not receive a positive genetic diagnosis and for whom their diagnostic odyssey continues. Also, it is possible that testing can allow inclusion into clinical trials for patients but this was outside the remit of this analysis and was not considered further. Any benefit or disbenefit not received by the actual patient was not included, such as other family members that can be tested for known mutations in patients with a positive diagnosis.

The health outcome was not measured using QALYs which is the preferred metric to inform resource allocation decisions across health care interventions across the NHS and is recommended by the National Institute for Health and Care Excellence (NICE). Using a QALY would have allowed a cost-utility analysis to have been performed which would have allowed comparison to the NICE QALY threshold to determine whether the use of exome sequencing tests compared to usual testing would constitute a cost effective use of resources. The use of QALYs in genomics has largely been limited to test-drug interventions often in cancer and has methodological limitations in genomics where it may also be important to capture non-health benefits.

Conclusions

This cost-effectiveness study has shown that whole exome sequencing-based virtual gene panel testing can be used cost–effectively within the diagnostic genetic testing strategy for constitutional genetics across a range of clinical scenarios and genetic disorders.

- The diagnostic yield ranged between 30% and 66.6% across the panels
- Sensitivity analyses showed that the largest driver of cost was the cost of the exome sequencing test (and the wider cost of all genetic tests included within the testing pathway)

Using targeted exome sequencing-based testing will likely lead to a larger budget requirement although this increase can be minimised through careful selection of patients most likely to benefit. If the cost of testing associated with using the exome approach as a near first-line test in a selected cohort of patients can be reduced it can potentially lead to a situation where no overall budget increase is required. This would, however, require selective test criteria and careful management coupled with data evaluation in order to determine whether such savings can be realised within the routine service.

If the cost of testing associated with using the exome approach as a near first-line test in a selected cohort of patients can be reduced, it can potentially lead to a situation where no overall budget increase is required.

Based on the data presented in this pilot, exome sequencing based testing could be focused in the clinical areas where the greatest utility is currently being observed with large increases in diagnostic yield. However, it should also be noted that if the testing strategy is focused on too narrow a patient group then the economy of scale required to reduce the price of exome sequencing testing to an acceptable per-test basis could be lost.

Two key strengths of this work are the appropriate use of testing strategies that were compared as both can easily be used within the NHS setting and also the appropriateness and direct applicability of the patient cohort to the wider NHS patient population that is likely to be the group in whom such testing is going to be used.

In conclusion, this work has shown that the cost of exome sequencing based tests and other genetic tests accounts for a significant portion of the overall budget required to attempt to establish a diagnosis in these 96 patients.

Ongoing work should focus on trying to reduce the cost of the exome sequencing test and potentially other baseline tests conducted in addition to exome sequencing, and to investigate the assumption that clinical work up can be reduced if a positive genetic diagnosis is achieved through the use of such testing earlier in the patient's diagnostic journey as a near first-line test.

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Appendix 1: Gene exome panels

DDG2P 1308

https://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/developmental-disorders-1308-gene-exome-panel-832/

Skeletal Dysplasia 222 gene exome panel

https://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/skeletal-dysplasia-222-gene-exome-panel-820/

Renal Disorders 220 gene exome panel

https://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/renal-disorders-220-gene-exome-panel-819/

Appendix 2: Disease sub panels

AD familial tubulo-interstitial nephritis with medullary cysts	*UMOD;*
Albright	*GNAS;*
Beals syndrome (*FBN2*)	*FBN2;*
Bloom syndrome	*BLM; FANCL; FANCB; RAD51C; SLX4; BRCA2; PALB2; FANCC; BRIP1; FANCD2; FANCM; FANCG; FANCA; FANCE; FANCF; FANCI; ERCC2; ERCC3; ERCC6; ERCC8; POLH; XPA; XPC; DDB2; ATM; WRN;*
Bowel cancer	*MLH1; MSH2; MSH6; PMS2; APC; MUTYH;*
Cardiomyopathy	*ABCC9; ACADVL; ACTC1; ACTN2; AGL; ANKRD1; ATP5E; BAG3; BRAF; CALR3; CASQ2; CAV3; CBL; COA5; CRYAB; CSRP3; CTF1; CTNNA3; DES; DMD; DMPK; DNAJC19; DOLK; DSC2; DSG2; DSP; DTNA; EMD; EYA4; FHL1; FHL2; FKTN; FOXRED1; FXN; GAA; GATAD1; GLA; GLB1; GUSB; HFE; HRAS; ILK; JPH2; JUP; KRAS; LAMA4; LAMP2; LDB3; LMNA; MAP2K1; MAP2K2; MRPL3; MYBPC3; MYH6; MYH7; MYL2; MYL3; MYLK2; MYOM1; MYOZ2; MYPN; NEBL; NEXN; NRAS; PDLIM3 PKP2 PLN; PRKAG2; PTPN11; RAF1; RBM20; RYR2; SCN5A; SCO2; SDHA; SGCD; SHOC2; SLC25A3; SOS1; SPRED1; SYNE1; SYNE2; TAZ; TCAP; TGFB3; TMEM43; TMEM70; TMPO; TNNC1; TNNI3; TNNT2; TPM1; TSFM; TTN; TTR; TXNRD2; VCL; XK;*
Cerebellar atrophy, Goldberg-Shprintzen	*KIAA1279;*
Coffin Siris	*ARID1A; ARID1B; SMARCA2; SMARCA4; SMARCB1; SMARCE1;*
Cohen syndrome	*VPS13B;*
Craniometaphyseal dysplasia	*ANKH; GJA1;*
Connective Tissue Disorders (CTD)	*ACTA2; ALDH18A1; ATP6V0A2; COL3A1; COL5A1; COL5A2; COL1A1; COL1A2; EFEMP2; ELN; FBN1; FBN2; FBLN5; GATA5; GORAB; LTBP4; MYH11; MYLK; NOTCH1; PYCR1; RIN2; SLC2A10; SMAD3; SMAD4; SKI; TNXB; TGFB2; TGFBR1; TGFBR2;*
Ectodermal dysplasia	*BRAF; CDH3; CTSC; EDA; EDAR; EDARADD; FERMT1; GJB6; IFT122; IFT43; KRT14; KRT85; MAP2K1; MAP2K2; MSX1; PKP1; PVRL1; TP63; TRPS1; TWIST2; WDR35;*
Epilepsy	*ALDH7A1; CACNA1A; CACNA1H; CACNB4; CASR; CHRNA2; CHRNA4; CHRNB2; CLCN2; CPA6; EFHC1; GABRA1; GABRB3; GABRD; GABRG2; GRIN2A; KCNMA1; KCNA1; KCNQ2; KCNQ3; KCNT1; LGI1; ME2; NIPA2; PRRT2; SCN1A; SCN1B; SCN2A; SCN8A; SCN9A; SLC2A1; TBC1D24;*
Extreme short stature - (*XRCC4*/lig1)	*XRCC4; PCNT; RNU4ATAC; ORC1; GHR; ATR; CENPJ; CEP152; RBBP8; OBSL1; CUL7; CCDC8; CEP63; SCKL3; NIN;*
Floating-Harbor syndrome	*SRCAP;*
FSGS	*NPHS1; NPHS2; WT1; PLCE1; CD2AP; MYO1E; COQ2; COQ6; TRPC6; PTPRO; APOL1; ACTN4; INF2; LMX1B; COL4A3; COL4A4; MYH9; ARHGAP24; PDSS2;*
Geleophysic	*ADAMTSL2; FBN1;*
Gordon syndrome	*PIEZO2;*
Holoprosencephaly	*CDON; FGF8; GLI2; GLI3; PTCH1; SHH; SIX3; TGIF1; ZIC2;*
Hypodontia	*MSX1; PAX9; WNT10A; ZNF22; LTBP3; EDA; AXIN2; RUNX2; NHS; SOX2;*
Hypogonadotrophic hypogonadism and anosmia	*CHD7; DUSP6; FGF17; FGF8; FGFR1; FLRT3; GNRH1; GNRHR; HS6ST1; IL17RD; KAL1; KISS1; KISS1R; NSMF; PROK2; PROKR2; SEMA3A; SPRY4; TAC3; TACR3; WDR11;*
IFAP-like	*MBTPS2;*
Kabuki	*KMT2D; KDM6A;*

Kabuki/Aarskog	*KMT2D; KDM6A; FGD1;*
KBG	*ANKRD11;*
Kleefstra	*EHMT1;*
Leber congenital amaurosis	*AIPL1; CEP290; CRB1; CRX; GUCY2D; IQCB1; KCNJ13; LCA5; LRAT; NMNAT1; RD3; RDH12; RDH5; RPE65; RPGRIP1; SPATA7;*
Metatropic dysplasia	*TRPV4;*
Mowat-Wilson	*ZEB2;*
Ochoa	*HPSE2;*
Orofacial digital syndrome 1	*OFD1; TCTN3; DDX59; TMEM216;*
OI type 1	*COL1A1; COL1A2; CRTAP; LEPRE1; PPIB; FKBP10; SERPINH1; SP7; PLOD2; LRP5; TMEM38B; CREB3L1; BMP1; SERPINF1; WNT1; IFITM5;*
Ostepetrosis	*TCIRG1; CLCN7; OSTM1; TNFSF11; PLEKHM1; CA2; IKBKG; FERMT3; CTSK; LEMD3; AMER1;*
Pancreatic insufficiency	*CASR; CFTR; COX4I1; CTRC; FOXA1; FOXA2; GATA6; PDX1; PRSS1; PRSS2; TMPRSS15; PTF1A; SDS; SPINK1; UBR1;*
Paraganglioma	*EGLN1; FH; PDE11A; PDE8B; PRKAR1A; SDHA; SDHC; SDHAF2; SDHB; SDHD;*
PVNH, cerebellar hypoplasia	*FLNA;*
RAS-opathy	*BRAF; CBL; HRAS; KRAS; MAP2K1; MAP2K2; NF1; NRAS; PTPN11; RAF1; SHOC2; SOS1; SPRED1; RIT1;*
Recessive retinitis pigmentosa	*ABCA4; ARL2BP; BBS1; BEST1; C2orf71; C8orf37; CERKL; CNGA1; CNGB1; CRB1; DHDDS; EMC1; EYS; FAM161A; FLVCR1; GNPTG; GPR125; IDH3B; IMPG2; KIAA1549; LRAT; MAK; MERTK; NEK2; NMNAT1; NR2E3; NRL; PDE6A; PDE6B; PDE6G; PRCD; PROM1; RBP3; RBP4; RDH12; RGR; RHO; RLBP1; RP1; RP1L1; RP2; RPE65; RPGR; SAG; SPATA7; TTC8; TULP1; USH2A; ZNF513; RECQL4; RECQL4;*
RECQL4	*RECQL4;*
Retinitis pigmentosa	*BEST1; CA4; CRX; FSCN2; GUCA1B; IMPDH1; KLHL7; NR2E3; NRL; PRPF3; PRPF31; PRPF6; PRPF8; PRPH2; RDH12; RGR; RHO; ROM1; RP1; RP2; RP9; RPE65; RPGR; SEMA4A; SNRNP200; TOPORS; ABCA4; ARL2BP; BBS1; C2orf71; C8orf37; CERKL; CNGA1; CNGB1; CRB1; DHDDS; EMC1; EYS; FAM161A; FLVCR1; GNPTG; GPR125; IDH3B; IMPG2; KIAA1549; LRAT; MAK; MERTK; NEK2; NMNAT1; PDE6A; PDE6B; PDE6G; PRCD; PROM1; RBP3; RBP4; RLBP1; RP1L1; SAG; SPATA7; TTC8; TULP1; USH2A; ZNF513;*
Rett-like	*MECP2; CDKL5; NTNG1; FOXG1;*
Rubinstein-Taybi	*CREBBP; EP300;*
SED	*COMP; COL9A1; COL9A2; COL9A3; MATN3; TRPV4; COL11A1; COL11A2; COL2A1;*
SED skeletal dysplasia	*COL11A1; COL11A2;*
SEDT	*TRAPPC2;*
Seip syndrome	*CAV1; AGPAT2; BSCL2; PTRF;*
SEMD-joint laxity	*KIF22; B3GALT6;*
Smith-Lemli-Opitz syndrome	*DHCR7;*
Smith-Magenis	*RAI1;*
Sotos-like	*NSD1; NFIX; EZH2; PTEN;*
Spondylocostal dysostosis	*DLL3; MESP2; LFNG;*
Spondyloenchondromatosis	*ACP5;*
Steiner syndrome	*MLL;*
Treacher Collins	*TCOF1; POLR1D; POLR1C; EFTUD2; SF3B4;*
Van der Woude syndrome	*IRF6; GRHL3;*
Wolfram	*WFS1; CISD2;*

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