Evaluation of new genetic tests for NHS services
March 2017

The recommendations from the Genetic Test Evaluation Working Group described in this document were endorsed by the UK Genetic Testing Network Clinical & Scientific Advisory Group at its meeting held in March 2017.

Relevant documentation will be provided for NHS England for the Clinical Priorities Advisory Group to review the resource implications for commissioning the recommended tests.

Scotland, Northern Ireland and Wales will receive separate documents on the resource implications relevant to their countries to assess new developments in genetic testing for their populations.

Key messages

4 new tests recommended for NHS service for 2018/19 in addition to new tests that will be recommended at the September 2017 CSAG meeting.

Of the new tests recommended **2 are expected to have less than, or equal to, 50 index cases per annum**

In addition to the clinical genetics specialty/CRG the tests range across:

- 11 specialties
- 6 Clinical Reference Groups (CRG)

Total additional **investment requested for the UK is £55,070** of which:

- £44,705 is required for medical genetics
- £10,365 is required for prescribed specialised services (excluding medical genetics)

Potential net savings/additional capacity released for the UK:
for medical genetics: £21,303
for prescribed services (excluding medical genetics): £19,047

Total potential net savings/additional capacity released for the UK NHS: £40,350

Context

The genetic test evaluation process (previously referred to as the Gene Dossier process) was developed by the UKGTN in 2003 in order to evaluate proposed laboratory genetic tests for specific genetic diseases for inclusion on the NHS Directory of Genetic Disorders/Genes for Diagnostic Testing (previously NHS Directory for Genetic Testing).

The UKGTN evaluates:

"any genetic test provided by a UKGTN member laboratory for NHS service provision for rare disorders that usually affect fewer than 1 in 2000 as described in the UK Rare Disease Strategy."

The burden of rare diseases was recognised in the Chief Medical Officer report 2009 stating that rare diseases, when considered collectively, are common and that "*a diagnosis of a rare disease has a huge impact, not just on the individual but also on their family. There are potential efficiencies in treatment if repetition of tests is avoided every time the patient sees another consultant*." These efficiencies are evidenced in the care pathway of the submissions to UKGTN for new genetic tests.

The update to the Strategy for UK Life Sciences (2012) championed genetic testing "*The UK has led the world in genetic and genomic science, and the Government is determined to provide a supportive environment, to ensure that the UK remains at the forefront of new innovations in this field, capitalising on this leadership for the benefit of UK patients, the NHS, and the UK economy*." This has led to the establishment of Genomics England to deliver whole genome sequencing in collaboration with NHS England and the 13 Genomic Medicine Centres.

The UK Strategy for Rare Diseases was published in December 2013. The strategy aims to drive forward understanding of rare disease and work to increase the prospects of finding effective and sustainable treatments and therapies and earlier diagnosis. It sets out 51 commitments. Implementation of these commitments is the responsibility of the four countries in the UK. A stakeholder forum has been established to oversee progress on implementation. A progress report was presented to Ministers to coincide with Rare Disease Day 2016 (28.02.16).

Recommendations to March 2017 CSAG for new genetic tests for commissioning year 2018/19

The UKGTN genetic test evaluation results and recommendations presented in this paper are for genetic tests that would not be evaluated by NICE as they are outside its selection criteria due to the rarity of the diseases being tested for.

The UKGTN Genetic Test Evaluation Working Group, in the period August 2016 to February 2017:

- **evaluated 4 new test applications (**gene dossiers)
- **recommends tests from 4 applications**, all of these impact on care pathways within prescribed services only.

To be noted:

- 3 applications are for tests that use Next Generation Sequencing (NGS) technologies
- of the 3 new test applications that use NGS, none of them had sub panels.
- 1 application was evaluated through the very rare disease process (less than 20 index cases a year and less than £5000 annual costs for index cases)
- 1 application was for diagnostic NIPD testing.

The recommendations are for a total of:

- 92 disorders
- 74 genes

The investment implications of the UKGTN recommendations for each new test is detailed in Appendix 1.

The clinical utility and consequences for patients if the tests were not available are provided in separate documentation.

It would be appropriate for Consultant Clinical Geneticists to request all the new tests although none of the tests would have Consultant Clinical Geneticists as the only referrer. The other specialties that have a test aligned are:

- Dermatology, Adult
- Dermatology, Paediatrics
- Endocrinology, Paediatrics
- Fetal Medicine
- Immunology, Adults
- Immunology, Paediatrics
- Neurology, Paediatrics
- Paediatrics
- Obstetrics
- Orthopaedic surgery, Adults
- Orthopaedic surgery, Paediatrics

Based on the types of referrers for each test and the nature of each disorder it is expected that the new tests would fall within 5 prescribed specialised services for England in addition to the medical genetics CRG. The CRGs (excluding E01: Medical Genetics) are listed below. Each CRG has only one test aligned to it with the exception of Paediatric Medicine that has two tests:

- A08: Dermatology (all ages)
- E03: Paediatric Medicine
- E04: Paediatric Neurosciences
- F06: Specialised Immunology & Allergy Services (all ages)
- E09: Specialised Women's Services

Healthcare Outcomes

UKGTN assess the benefits to patients as a result of new genetic tests. The categories for healthcare outcomes are summarised below and Appendix 2 provides details about the expected outcomes for each test.

1. Genetic testing alerts significant clinical co-morbidities
2. Reduces mortality/saves lives
3. Avoids irreversible harm
4. Avoids diagnostic procedures/tests (some of which may be invasive) and/or multiple hospital visits
5. Avoids incorrect management (e.g. medication or treatment) that could be harmful
6. Confirms targeted therapy/management
7. Earlier diagnosis allowing commencement of treatment earlier with associated improved prognosis
8. Enables access to educational and social support
9. At risk family members that test negative for a familial mutation can be discharged from follow up
10. At risk family members that test positive for a familial mutation have appropriate follow up.

Investment for new genetic tests for NHS service from 2018/19

The table in appendix 1 listing the individual new tests being recommended shows estimated investment required for clinical genetics separately from the investment requirements for specialties outside of clinical genetics. This has been calculated based on expected activity and deducting any savings from tests or procedures that are no longer required in the patient pathway to diagnosis. Full details of how the investments and savings have been calculated are available in appendix 3.

Table 1 below shows the investment required for clinical genetics and for other prescribed services. It is recognised that the devolved nations do not have CRGs and these figures can be used to inform their relevant commissioning bodies.

Table 1. Investment for the UK for clinical genetics and other prescribed specialised services.

Specialty/CRG/CCG	Investment
clinical genetics activity ONLY	**£44,705**
CRG specialties activity EXCLUDING clinical genetics	**£10,365**
TOTAL	**£55,070**

None of the tests are provided on a cost neutral basis.

Two tests require investment with no expected savings in the diagnostic pathway to offset this investment.

There are 2 tests that show investment and savings/ efficiencies. This usually occurs when there are savings for index cases (usually due to a decrease in other tests required to diagnose if the genetic test is introduced earlier in the diagnostic care pathway or because the NGS test replaces sequential testing) but new costs as there is an expectation that a greater number of at risk family members could have testing due to an increase in the number of index cases identified (due to a wider breadth of genes analysed).

Two of the tests are targeted panels and one of these includes genes that are already available for testing as single gene tests. The new panel test will, for most cases, replace the need for single gene testing. Although in some instances the single gene testing may still be a preferred option where the clinical phenotype is obvious for the condition.

The new genetic tests that cost less than the current diagnostic tests can be introduced at cost saving and overall there is a UK net saving for the CRGs, and equivalent organisations in the devolved nations, of £40,350.

The net savings/released capacity for the United Kingdom for medical genetics activity is shown in table 2 (over the page). For England this is expected to align to the Medical Genetics CRG.

Table 2. Estimated net savings/released capacity for new UKGTN recommended testing services for clinical genetics **for all UK countries**

Country	POPULATION	POTENTIAL NET SAVINGS Medical Genetics only
England	**54,786,327**	£17,925
Wales	**3,099,086**	£1,014
Scotland	**5,373,000**	£1,758
Northern Ireland	**1,851,621**	£606

The total estimated potential net savings/released capacity for England for the clinical genetics specialty only if the new UKGTN recommended tests were implemented, are listed by region in Table 3.

Table 3. Estimated potential net savings for new UKGTN recommended testing services for Medical Genetics CRG **for England**.

Country & Region (England)	POPULATION	POTENTIAL NET SAVINGS Medical Genetics only
England	54,786,327	£17,925
North	15,189,032	£4,970
Midlands and East	16,504,489	£5,400
London	8,673,713	£2,838
South	14,419,093	£4,718

The net savings/released capacity for England and the devolved countries for activity from other specialties excluding clinical genetics (in England for other prescribed services excluding the Medical Genetics CRG activities) is shown in table 4.

Table 4. Estimated net savings for new UKGTN recommended testing services for other specialties excluding medical genetics **for all UK nations**

Country	POPULATION	POTENTIAL NET SAVINGS CRGs excluding Medical Genetics
England	**54,786,327**	£16,027
Wales	**3,099,086**	£907
Scotland	**5,373,000**	£1,572
Northern Ireland	**1,851,621**	£542

The net savings/released capacity for new recommended tests across CRGs excluding medical genetics for England only by region are shown in Table 5.

Table 5. Estimated net savings for new UKGTN recommended testing services across all specialised services (excluding clinical genetics) **for England**.

Country & Region (England)	POPULATION	POTENTIAL NET SAVINGS CRGs excluding Medical Genetics
England	**54,786,327**	£16,027
North	15,189,032	£4,443
Midlands and East	16,504,489	£4,828
London	8,673,713	£2,537
South	14,419,093	£4,218

The total estimated investment, savings and net savings across all funding streams for each devolved nation is shown in table 6.

Table 6. Estimated investment, potential savings/efficiencies and net costs for all activity across the home nations

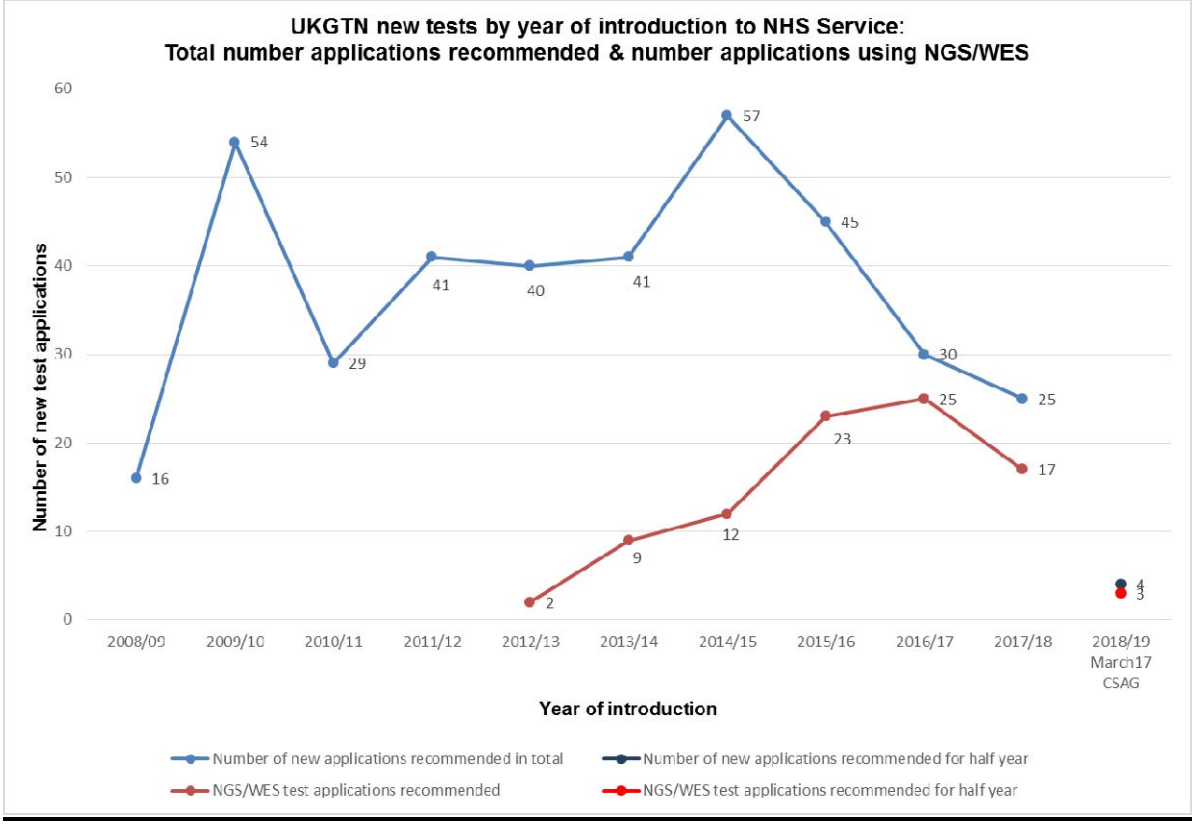
	Home Nation			
	England	**Scotland**	**Northern Ireland**	**Wales**
Investment	£46,338	£4,545	£1,566	£2,621
Savings	£80,290	£7,874	£2,714	£4,542
Net Savings	£33,952	£3,329	£1,148	£1,921

Investment/Savings have not been provided for testing for those laboratories that requested to be an additional provider as the resource is already available for these tests.

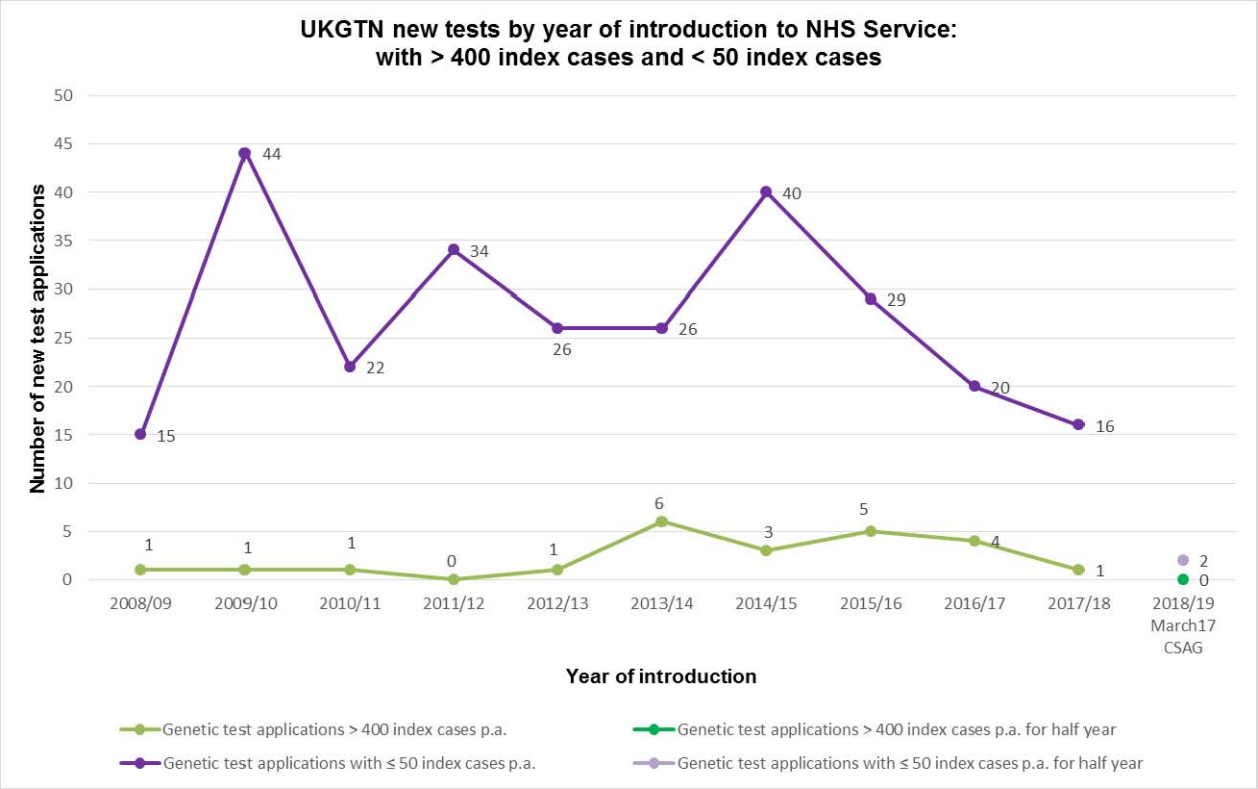
Services to be commissioned from 1st April 2018. The new test service information will be available from the website http://ukgtn.nhs.uk/find-a-test/. Information about the disorders that the tests are for and the clinical utility of each test are provided in appendix 4.

Trend Analysis

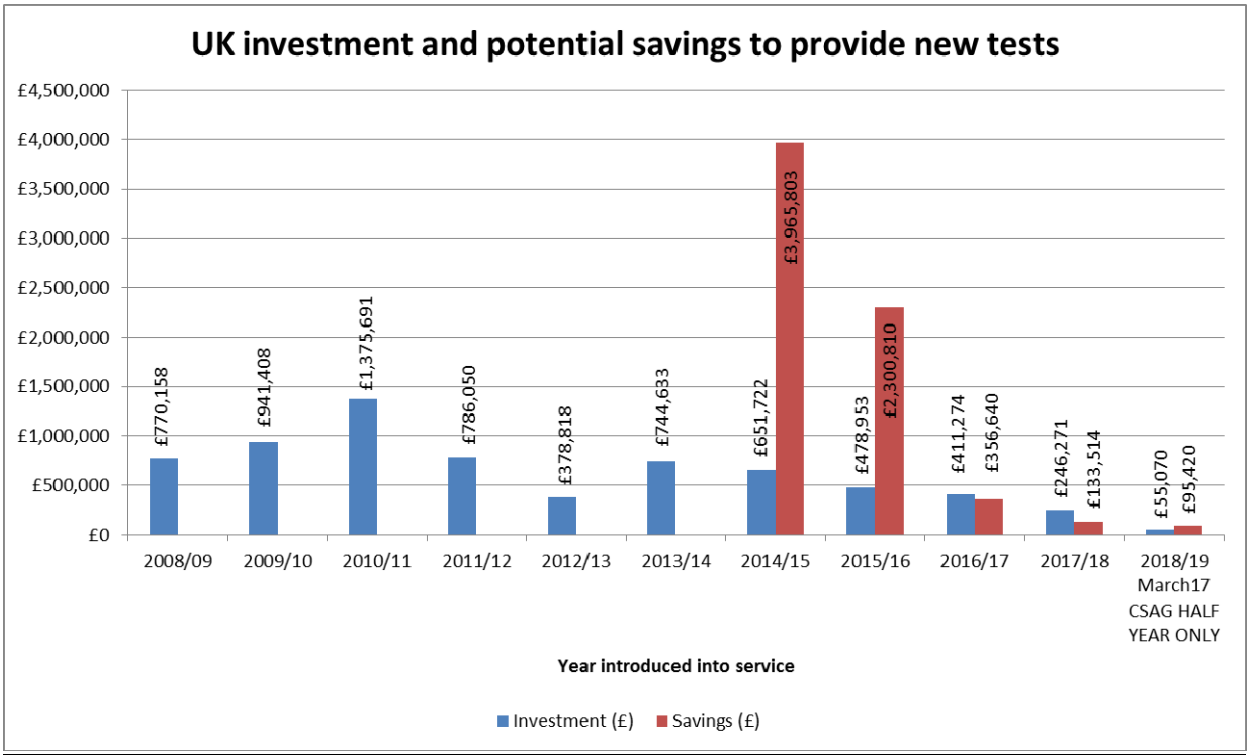
The graph below details the number of new test applications received since 2007 for commissioning from 2008/09. There has been a steady increase in applications over the years followed by a recent decline due in part to an increasing number of large NGS panel test applications.



The graph below details the number of new test applications recommended for NHS service by year of introduction based on the expected number of index cases in any one year. It is expected that the activity for index cases for the majority of tests being introduced will be for less than 50 a year.



The figures shown in the chart below are indicating the total investment per annum for the genetic tests to be implemented. Tests introduced from 2014/15 also show total potential savings that could occur.



The Genetic Test Evaluation Process

Overview

The genetic test evaluation process (previously referred to as the Gene Dossier process) was developed by the UKGTN in 2003 in order to evaluate proposed laboratory genetic tests for specific genetic diseases for inclusion on the NHS Directory of Genetic Disorders/Genes for Diagnostic Testing (previously NHS Directory for Genetic Testing). Once a test is on the Directory it is recommended to be considered for NHS funding. The Directory lists disease and gene combinations for which tests are available and NGS panel tests that have been agreed as appropriate for clinical use, from member laboratories. Information about the testing services provided and the laboratories providing them are available from the online database on the UKGTN website. The process ensures that the decision regarding the recommendation of a test is explicit, transparent and based on evidence. The genetic test evaluation documents (Gene Dossier and Additional Provider forms) and a description of the process can be found at http://ukgtn.nhs.uk/resources/genetic-test-evaluation-process/.

The genetic test evaluation form (gene dossier)

The process requires laboratories to submit a form called a 'gene dossier' for evaluation by the Genetic Test Evaluation Working Group (GTEWG). The membership of this group includes professionals from Clinical Genetics, clinical laboratory genetics, Public Health, commissioning and patient groups. The gene dossier provides a standardised format for the evaluation of the key information about a genetic test including analytical validity, clinical validity and clinical utility. Laboratories submit a shortened version of the form, called an additional provider form, to request listing of a test under their laboratory on the UKGTN website where the test is already on the NHS Directory of Genetic Disorders/Genes or on the UKGTN website.

Testing Criteria

Every application for a new test that is submitted has to include testing criteria. The UKGTN developed the concept of testing criteria as part of the new test application process. Testing Criteria define the appropriateness of a genetic test referral, and it is intended that the test is only carried out in accordance with the criteria as set out in the gene dossier and approved by the UKGTN Clinical and Scientific Advisory Group. Testing Criteria should include only those data that are specified within the gene dossier, and should not be confused with any other information that a provider laboratory may wish to have for research or any other reasons. The additional benefit of these criteria is that they can inform clinicians' decisions about which investigations are suitable for their patients. The types of referrers on the Testing Criteria are used to inform the specialties that would order the tests and the associated CRGs.

In addition to developing Testing Criteria as part of the test evaluation process, the GTEWG also develops Testing Criteria for tests that have been on the NHS Directory of Genetic Disorders/Genes prior to the introduction of Testing Criteria. The UKGTN project team organises conferences/workshops on specific disorders for scientists and clinicians in order to develop consensus Testing Criteria. This promotes a consistent approach to genetic test provision for these conditions throughout the UK. The UKGTN has used this method to develop Testing Criteria for Cystic Fibrosis, Fragile X, Marfan syndrome and familial breast and ovarian cancer.

Tests that the UKGTN will evaluate

The UKGTN will evaluate any new genetic test that a UKGTN laboratory member wishes to provide and have listed on the NHS Directory of Genetic Disorders/Genes for Diagnostic Testing. For the UKGTN genetic test evaluation purposes, prior to April 2013, a genetic test was defined as any test for NHS service provision by a UKGTN member laboratory which required funding by specialised commissioning arrangements, supporting provision of clinical genetics services as defined in the national definition set for medical genetics services. Since April 2013, the definition of a genetic test for UKGTN evaluation has been expanded to include tests for any prescribed specialised service.

The Evaluation

It is recommended that new test applications are completed by the UKGTN laboratories in collaboration with clinical colleagues with relevant specialist expertise. The GTEWG undertakes the evaluation of the proposed new tests.

The evaluation is based on the ACCE (**A**nalytical validity, **C**linical validity, **C**linical Utility & **E**thical, Legal and Social) framework[1] and takes into account the following:

1. The seriousness of the condition
2. The prevalence of the condition
3. The purpose of the test- diagnosis, treatment, prognosis and management, presymptomatic testing, risk assessment
4. The technical details of the test
5. The context in which the test is to be used- defined population groups
6. The characteristics of the test- the clinical sensitivity, specificity and predictive value
7. The clinical utility of the test- how it adds to patient management and the availability of alternative diagnostic procedures
8. Ethical, legal and social considerations
9. The price of the test

Test applications are also assessed for specified healthcare outcomes.

Commissioning

The results of the evaluation are presented to the UKGTN Clinical and Scientific Advisory Group (previously UKGTN Steering Group) for endorsement. Following this endorsement the recommendations are reported to NHS England and equivalent organisations in Wales, Scotland and Northern Ireland. Each devolved nation follows its own process to consider adoption of the tests. UKGTN approved tests are added to the NHS Directory of Genetic Disorders/Genes for Diagnostic Testing and the UKGTN online database. Both of these resources are publically available from the UKGTN website (www.ukgtn.nhs.uk).

Frequency of evaluation cycles

Prior to 2014 the process was carried out annually (over a nine month period from submission to recommendations being made) with recommendations being made to the September CSAG meeting. From 2014 the process became biannual with recommendations being made to both the March and September CSAG meetings. The two deadlines for gene dossier submissions to UKGTN are 31st January (for recommendations made to the September CSAG within the same year) and 31st July (for recommendations made to the March CSAG in the following year).

Monitoring the introduction of UKGTN recommended new tests

The UKGTN monitors the activity and funding required for new tests that have been approved two years after they have been recommended for national NHS service. This provides a comparison of the real activity and costs against those predicted in the application forms. This is shared with the Medical Genetics Clinical Reference Group and any large differences identified as part of this national audit are investigated by UKGTN to establish the reasons for the disparity.

[1] Haddow J, Palomaki G. ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests. Human Genome Epidemiology. Khoury M, Little J, Burke W, eds. Oxford: Oxford University Press, 2004; 217-233

NHS

UK Genetic Testing Network

Appendix 1

Evaluation number as assigned during the process	Test Name	Clinical Collaborator	Laboratory	Cost per test for index cases	Cost per test for family members	Expected annual referrals for index cases	Expected annual referrals for family members	Types of referrers on testing criteria All referrers are at Consultant Level	Split of activity based on CRG	Estimate of total annual INVESTMENT based on expected numbers	Estimate of annual INVESTMENT from clinical genetics	Estimate of annual INVESTMENT from mainstream specialty outside of clinical genetics	Estimate of total annual SAVINGS based on expected numbers	Estimate of annual SAVINGS from clinical genetics	Estimate of annual SAVINGS from mainstream specialty outside of clinical genetics	Where thare are SAVINGS: Does the test replace other tests?
NEW TEST RECOMMENDATIONS TO BE CONSIDERED FOR FUNDING																
#345 (very rare)	Microcephalic Osteodysplastic Primordial Dwarfism, Type II; MOPD2	Professor Andrew Jackson	**Edinburgh RGC**	£400	£140	20	40	Clinical Geneticist Paediatric Neurologist Paediatric Endocrinologist	E01: Medical Genetics (I=16, F=32) E04. Paediatric Neurosciences (I=2, F=4) E03. Paediatric Medicine (I=2, F=4)	£5,600	£4,480	E04: £560 A03: £560	£17,960	£14,368	E04: £1796 A03: £1796	Eliminates the need for MRI every two years for patients where the test is negative (no mutation found).
#349	Ectodermal Dysplasia Plus 70 gene panel	Professor Angus Clarke	**Cardiff RGC**	£750	£160	60	40	Clinical Geneticist Dermatologist (Adult & Paediatric) Immunologist (Adult & Paediatric)	E01: Medical Genetics (I=40, F=40) A08: Dermatology (all ages) (I=13, F=0) F06: Specialised Immunology & Allergy Services (all ages) (I=7, F=0)	£2,080	£2,080	n/a	£77,460	£51,640	A08: £16,783 F06: £9,037	Reduces need for sequential single gene testing & associated clinical appts. No longer need skin biopsy or sweat test.. If gene test does not find a mutation then a skin biopsy would be done.
#338	Hereditary Multiple Osteochondromas 2 Gene Panel	Dr Amanda Collins	**Salisbury RGC**	£665	£175	40	15	Clinical Geneticist Paediatrician Adult Orthopaedic Surgeon Paediatric Orthopaedic Surgeon	E01: Medical Genetics (I=30, F=15) E03. Paediatric Medicine (I=10, F=0) *To note: Paed Orthopaedics is encompassed in Paed Medicine CRG and Adult Orthopaedic is encompassed in medical genetics due to the Specialised Orthopaedic CRG being closed in 2016.*	£29,225	£22,575	E03: £6,650	n/a	n/a	n/a	n/a
NON-INVASIVE PRENATAL DIAGNOSIS (NIPD) - FOR NEW CONDITIONS																
#350	Spinal Muscular Atrophy (SMA) (NIPD - Diagnostic Testing)	Dr Trevor Cole Dr Denise Williams	**Birmingham RGC**	£1,200	n/a	70	n/a	Clinical Geneticist Consultant in Fetal Medicine Obstetrician	E01: Medical Genetics (I=60) E09: Specialised Women's Services (I=10)	£18,165	£15,570	£2,595	n/a	n/a	n/a	n/a
									TOTAL	**£55,070**	**£44,705**	**£10,365**	**£95,420**	**£66,008**	**£29,412**	
GENE DOSSIERS CONVERTED TO ADDITIONAL PROVIDER SUBMISSIONS																
#351	Genetic Epilepsy 104 Gene Panel		**Glasgow RGC**													
NEW TESTS NOT RECOMMENDED																
GENE DOSSIERS SUBMITTED BUT FURTHER VALIDATION REQUIRED																
#346	Congenital Eye Disorders 449 Gene **Exome** Panel consisting of 7 sub panels: **Sub panel 1:** MAC (86) **Sub panel 2:** ASD and Glaucoma (59) **Sub panel 3:** Retinal dystrophies (236) **Sub panel 4:** Albinism (15) **Sub panel 5:** Cataract and lens-associated (91) **Sub panel 6:** Optic atrophy (13) **Sub panel 7:** Complex Strabismus (10)		**London North East RGC** **GOSH**													
#347	Dermatology 261 Gene Exome Panel consisting of 10 sub panels: **Sub panel 1:** Mendelian disorders of cornification / palmoplantar keratodermas (50 genes) **Sub panel 2:** Ectodermal disorders (62 genes) **Sub panel 3:** Connective/adipose tissue disorders (33 genes) **Sub panel 4:** RASopathies and Pigmentary disorders (78 genes) **Sub panel 5:** Vascular disorders (20 genes) **Sub panel 6:** Mosaic disorders (19 genes) **Sub panel 7:** Inflammatory skin disorders (25 genes) **Sub panel 8:** Progeria (10 genes) **Sub panel 9:** DNA repair disorders (34 genes) **Sub panel 10:** Epidermolysis bullosa/skin fragility (26 genes)		**London North East RGC** **GOSH**													
#348	Neurogenetic Movement Disorders 251 gene panel consisting of 6 sub panels: **Sub panel 1:** Ataxia (181 genes) **Sub panel 2:** Chorea (23 genes) **Sub panel 3:** Dystonia (58 genes) **Sub panel 4:** Episodic Ataxia (11 genes) **Sub panel 5:** Familial Hemiplegic Migraine (11 genes) **Sub panel 6:** Parkinsons (52 genes)		**Sheffield RGC**													

Appendix 2

Tests aligned to Healthcare Outcomes

Evaluation number as assigned during the process	Test Name	Laboratory	1.Alerts significant clinical co-morbidities	2.Reduces mortality/ saves lives	3.Avoids diagnostic procedures/ tests (some of which may be invasive) and/ or multiple hospital appointments	4.Confirms targeted therapy/ management	5.Earlier diagnosis allowing commencement of treatment earlier with associated improved prognosis	6.Avoids irreversible harm	7.Enables access to educational and social support	8. At risk family members that test negative for a familial mutation can be discharged from follow up	9.At risk family members that test positive for a familial mutation have appropriate follow up	10.Avoids incorrect management (eg medication or treatment) that could be harmful)
RECOMMENDATIONS TO BE CONSIDERED FOR FUNDING												
#345 (very rare)	Microcephalic Osteodysplastic Primordial Dwarfism, Type II; MOPD2	Edinburgh RGC	●	●	●	●			●	●	●	●
#349	Ectodermal Dysplasia Plus 70 gene panel	Cardiff RGC	●		●		●		●	●	●	
#338	Hereditary Multiple Osteochondromas 2 Gene Panel	Salisbury RGC	●		●		●	●	●	●	●	●
#350	Spinal Muscular Atrophy (SMA) (NIPD - Diagnostic Testing)	Birmingham RGC		●	●	●		●				

Appendix 3

Detail of how the investment and savings have been calculated

1. For each test the investment/savings information derived from Questions 38 and 39 in the test application form (gene dossier) are aligned to the test. These investment/savings are calculated by firstly determining if there are any tests/procedures that would no longer be required to make a diagnosis because the new gene test being proposed would take place at an earlier stage in the pathway (Q38 in the Gene Dossier). For example, the introduction of a 95 gene panel for syndromic and non syndromic hearing loss would allow those patients who are recognised early enough in their pathway to diagnosis to be offered the genetic test instead of having sequential gene tests for individual genes already available and repeated ECGs, ERGs & renal ultrasounds as part of the diagnostic pathway although these may still be required as part of management after diagnosis. Any savings from tests/procedures that would no longer be required to make a diagnosis are off set against the full costs to provide gene testing based on estimated annual activity and the cost per gene test (detailed in Q39 in the Gene Dossier).

2. If there are savings for the index cases and family members then this will show as an overall saving across the whole test.

3. If there is an investment for the index cases and family members then this will show as an overall investment across the whole test.

4. If there are investments for the index cases and savings for family members or vice versa then the test will show both savings and investments on the summary sheet.

5. The savings /investments for index cases are then proportioned out across the clinical genetics specialty and the other specialties based on the estimated activity for index cases. Separately the savings/investments for family member testing are proportioned across the specialties based on estimated activity for family member testing for each specialty. The estimated activity per specialty is detailed in the financial section of the Gene Dossier.

6. The allocation of investment/savings for each UK country is proportioned based on the UK population and the populations of each country.

Appendix 4
Descriptions of the disorders that the tests are for and the utility for providing testing in the NHS

Evaluation No	Test Name	Laboratory	Disease Description	Utility of test in the NHS	Consequences of not testing
#338	**Hereditary Multiple Osteochondromas 2 Gene Panel**	**Salisbury RGC**	• Hereditary Multiple Osteochondromas (HMO) is characterised by the presence of recurrent multiple bony growths (osteochondromas) which develop during childhood. • These growths can cause significant bone deformity, restrict movement and cause considerable pain and discomfort; if present on the spine, they have the potential to cause neurological damage. • These bony growths also can become cancerous in some cases. • Patients often require multiple surgical procedures to treat the bony growths.	• Mutation detection will confirm the diagnosis and identify which gene is responsible. • For an affected patient, offspring risks are then known and prenatal diagnosis or PGD is possible. • There is some evidence that patients with *EXT2* mutations have less severe disease, and if proven, future surveillance might be guided by the genotype.	• Parents would not have choices regarding prenatal diagnosis and PGD, and young family members might have unnecessary appointments and investigations. • For a *de novo* case, diagnosis, surveillance and appropriate early interventions (e.g. for wrist deformity) might be delayed. • The bony growths may not appear until mid childhood causing understandable anxiety if not diagnosed in a timely manner. • The emergence of a clear genotype/phenotype correlation in the future may impact on patient management in the future.
#345 (very rare)	**Microcephalic Osteodysplastic Primordial Dwarfism, Type II; MOPD2**	**Edinburgh RGC**	• Microcephalic osteodysplastic primordial dwarfism type II (MOPDII) is an autosomal recessive disorder of extreme growth failure, which starts before birth. • Growth delay continues after birth, leading to severe proportionate short stature (final adult height is ~3 feet) and a small head (Willems et al., 2010). • Patients often have normal	• There are significant co-morbidities associated with MOPDII. • Complications include severe insulin resistance (approximately 50% are diabetic) and cerebrovascular disease such as Moyamoya disease and brain aneurysms (>50%). • Confirming a diagnosis of	• Diagnosis would not be made and the disease may not be managed correctly in particular with regards to known co-morbidities. • Further invasive /inappropriate testing may be carried out in an attempt to find an explanation for the family. • Options for early prenatal diagnosis would not be available if requested. Further affected children could be born (recurrence risk is 1 in 4 if both parents are carriers).

			intelligence or mild learning difficulties. • All MOPDII patients have *PCNT* mutations. • Patients with MOPDII are at risk of additional complications such as diabetes and brain aneurysms. • A genetic diagnosis of MOPDII can therefore enable appropriate clinical management of these patients, including regular monitoring for signs of insulin resistance and blood vessel abnormalities.	MOPDII, by genetic testing of *PCNT*, will allow patients to receive appropriate surveillance and earlier management for complications. • Excluding sequence variants in *PCNT* is helpful to support decisions not to perform regular MRI screening.	
#349	**Ectodermal Dysplasia Plus 70 Gene Panel**	**Cardiff RGC**	• Ectodermal Dysplasia (ED) is a group of closely related conditions involving more than 150 different syndromes. The clinical effects can be highly variable both within a family and between different types of ED, but often include: • life-threatening infection; • a permanent susceptibility to overheating; • a tendency to chest infection, chronic lung disease, eczema, asthma and atopy. • associated malformations such as cleft palate, ectrodactyly (split hands and feet), absent	• The test will help achieve accurate genetic diagnosis and establish inheritance patterns. • This will aid in making informed decisions about management, prognosis and monitoring of patients for potential complications as well as other associated symptoms reported in the various syndromes. • This will also help to provide advice for family members regarding reproductive risks. • Targeted treatments are being developed for ED which will only be applicable to certain mutations/genetic loci.	• It could potentially take considerably longer for a confirmed diagnosis with continued uncertainty about nature of child's condition and laborious sequential testing of single genes. • Some patients with ED would not receive a diagnosis. • Family members would not have accurate recurrence risks affecting reproductive choices. • Patients would not be aware of any complications specific to this form of ED which could be minimised by early intervention.

			Meibomian glands leading to dry sticky eye and ankyloblepharon (fusion of the eyelids)(in p63-related ED); • significant malformation of teeth including poorly developed, absent or misplaced teeth (hypodontia, oligodontia or anodontia). • The well recognised and most difficult aspect of coping with ED, is the stigmatisation to which many affected individuals are subject, especially in adolescence.		
#350	**Spinal Muscular Atrophy (NIPD – Diagnostic Testing)**	**Birmingham RGC**	• Spinal muscular atrophy (SMA) is an inherited progressive muscle-wasting condition which may affect a person's ability to crawl and walk, to move their arms, hands, head and neck, as well as their breathing and swallowing. • There are three main types of SMA defined by the severity of symptoms and the age of onset. • In its most severe form (SMA type 1), symptoms occur before six months of age and children do not survive beyond their first year due to recurrent respiratory infections. • The symptoms in children with SMA type 3 can be	• Couples would often have significant concern about the birth of a child with SMA but may be reluctant to pursue invasive predictive testing because of the associated risk of miscarriage. • This non-invasive test will therefore have several benefits: 1. Enable a pregnancy in couples who would not consider having an affected child but would decline an invasive test with a miscarriage risk and do not have access to pre-implantation genetic diagnosis (PGD) or who do not wish to or are unable to undergo PGD. 2. Reduce number of	• The alternative to non-invasive prenatal diagnosis (NIPD) would be for all women carrying a baby at risk of SMA to undergo invasive testing (CVS / Amnio) to determine whether the baby is affected or not. • These invasive procedures each carry a risk of miscarriage. In all cases invasive testing could be avoided if the pregnancy were tested by NIPD. • Patients would have to wait longer to know if their baby was affected with SMA.

			quite variable; some might be able to walk independently while others require life-long support.	miscarried but unaffected babies. 3. Enable couples who are pregnant but would decline a test with a miscarriage risk to have pre-natal diagnosis. 4. Enables earlier prenatal diagnosis.	