UK Genetic Testing Network

Evaluation of new genetic tests for NHS services
September 2016

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 September 2016.

The UKGTN will liaise with NHS England to determine the process requirements to review the resource implications for the commissioning process.

The recommendations have been shared with representatives from Scotland, Northern Ireland and Wales who have been asked to note these recommendations when assessing new developments in genetic testing for their populations.

Key messages

11 new tests recommended for NHS service for 2017/18 in addition to tests that were recommended and approved at the March 2016 CSAG meeting.

Of the new tests recommended **4 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:

- 15 specialties
- 9 Clinical Reference Groups (CRG)
- Clinical Commissioning Group (CCG)*

Total additional **investment requested for the UK is £203,116** of which:

- £56,076 is required for medical genetics
- £127,497 is required for prescribed specialised services (excluding medical genetics)
- £19,543 is required for the CCGs

Potential net investment for the UK:
Net costs for medical genetics: £38,973
Net costs for prescribed services (excluding medical genetics): £36,586

Total potential net investment for the UK NHS: £95,102

**The CCG is in relation to Paediatric Dentistry, Paediatric Dental Surgery, Paediatric & Adult Neurology & Psychiatry

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 September 2016 CSAG for new genetic tests for commissioning year 2017/18

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 March to August 2016:

- **evaluated 12 new test applications (**gene dossiers)
- **recommends 11** new tests, all of these impact on care pathways within prescribed services with 4 also having an option to be requested from clinics (Paediatric Dentistry, Paediatric Dental Surgery, Paediatric & Adult Neurology & Psychiatry) funded by CCGs

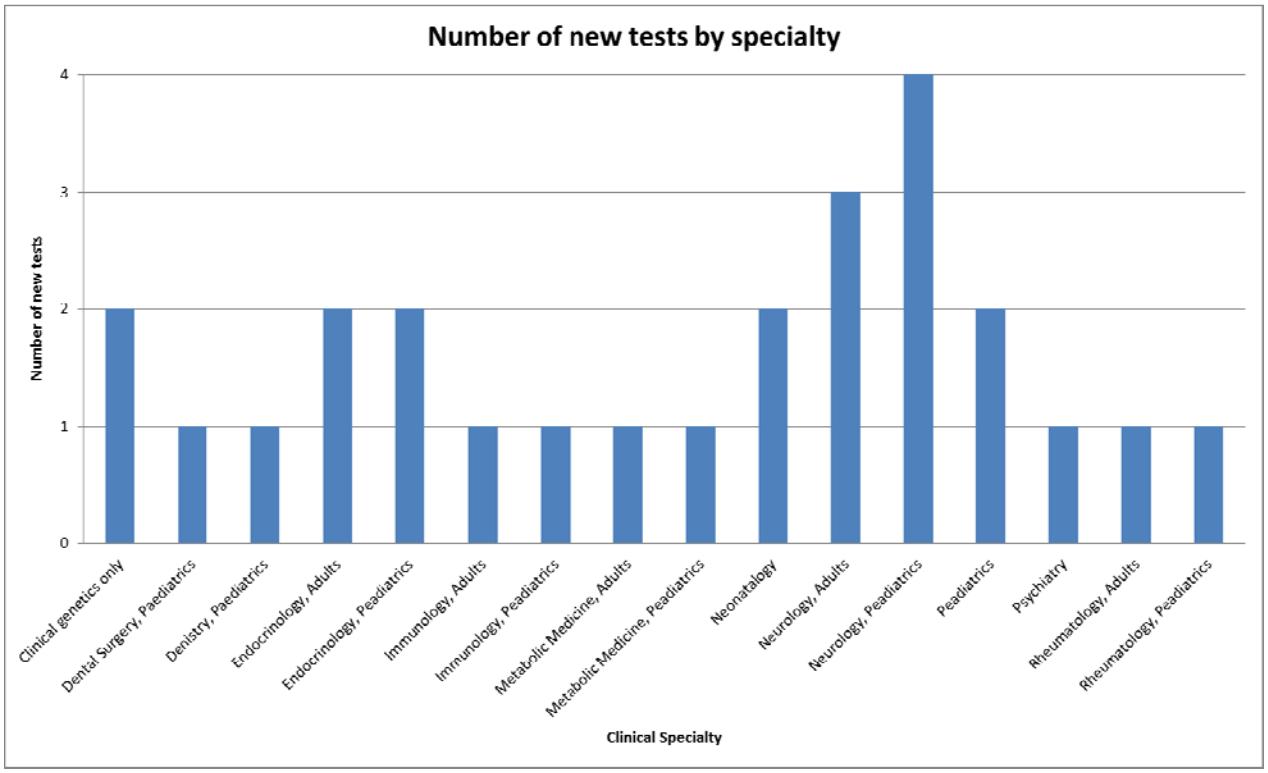
To be noted:

- 7 recommendations are panel tests that use Next Generation Sequencing (NGS)
- of the 7 new test applications that using NGS, 1 has 8 sub panel tests, 1 has 2 sub panels and 1 has 4 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)

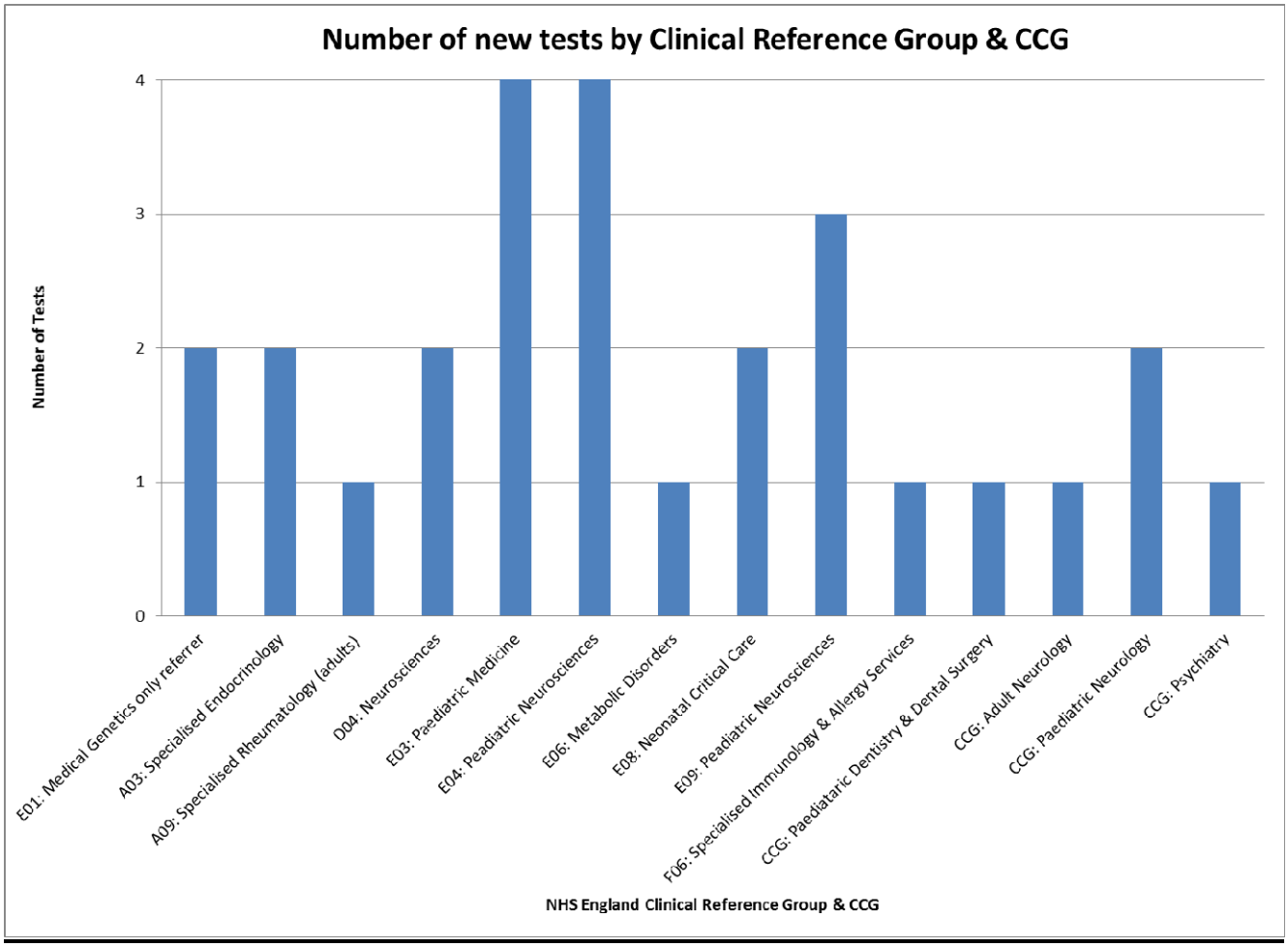
The cost implications of the UKGTN recommendations for new tests are detailed in Appendix 1.

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

The number of new tests by specialty are indicated in the bar chart below. It would be appropriate for Consultant Clinical Geneticists to request all the new tests but 2 have Consultant Clinical Geneticists as the only referrer.



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 9 prescribed specialised services for England in addition to the medical genetics CRG and those funded by CCGs. The number of tests by CRG and CCG is shown in the bar chart on page 4.



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.

Funding for new genetic tests for NHS service from 2017/18

The table in appendix 1 listing the individual new tests being recommended shows estimated funding required for clinical genetics separately from the funding requirements for specialties outside of clinical genetics and for CCGs. 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 costs and savings have been calculated are available in appendix 3.

Table 1 below shows the investment required for clinical genetics and other prescribed services excluding clinical genetics and for CCGs. It is recognised that the devolved nations do not have CCGs 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	**£56,076**
CRG specialties activity EXCLUDING clinical genetics	**£127,497**
CCG ONLY	**£19,543**
TOTAL	**£203,116**

Four tests are provided on a cost neutral basis as they have the potential to replace other diagnostic tests and procedures that are similar to the cost of providing the new genetic test.

There are 2 tests that show both costs and cost savings/ efficiencies. This 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).

Seven tests are NGS panels and all of them have a number of genes on the panel that are already available for testing as either single gene or as part of multi gene tests using Sanger Sequencing or other NGS tests. In some cases the panel tests replace these and in other cases they are used alongside them. For the latter scenario this would usually be where the clinical phenotype is obvious for a condition and the single gene Sanger test would remain the preferred option.

Tests that cost less than the current diagnostic tests can be introduced at cost saving. There are potential net costs for the CRGs of £75,559. There is a cost for CCGs of £19,543 with no savings assigned. Consequently the overall net costs irrespective of funding route is £95,102.

The net costs for England and the devolved countries for medical genetics CRG activity is shown in table 2 (over the page). It is recognised that CRGs apply to commissioning in England only and it is suggested that devolved nations use these details to apply to the equivalent commissioning bodies in Scotland, Northern Ireland and Wales.

Table 2. Estimated net costs for new UKGTN recommended testing services for clinical genetics CRG **for all UK countries**

Country	POPULATION	POTENTIAL NET COSTS Medical Genetics only
England	**54,316,618**	£32,771
Wales	**3,092,036**	£1,866
Scotland	**5,347,600**	£3,226
Northern Ireland	**1,840,498**	£1,110

The total estimated potential net costs 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 costs for new UKGTN recommended testing services for Clinical Genetics CRG **for England**.

Country & Region (England)	POPULATION	POTENTIAL NET COSTS Medical Genetics only
England	**54,316,618**	£32,771
North	15,111,728	£9,117
Midlands and East	16,369,080	£9,876
London	8,538,689	£5,152
South	14,297,121	£8,626

The net costs for England and the devolved countries for CRGs excluding clinical genetics and CCGs is shown in table 4.

Table 4. Estimated net costs for new UKGTN recommended testing services for CRGs excluding clinical genetics & CCGs **for all UK nations**

Country	POPULATION	POTENTIAL NET COSTS CRGs excluding Medical Genetics
England	**54,316,618**	£30,764
Wales	**3,092,036**	£1,751
Scotland	**5,347,600**	£3,029
Northern Ireland	**1,840,498**	£1,042

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

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

Country & Region (England)	POPULATION	POTENTIAL NET COSTS CRGs excluding Medical Genetics
England	**54,316,618**	£30,764
North	15,111,728	£8,559
Midlands and East	16,369,080	£9,271
London	8,538,689	£4,836
South	14,297,121	£8,098

The total estimated investment, savings and net costs 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

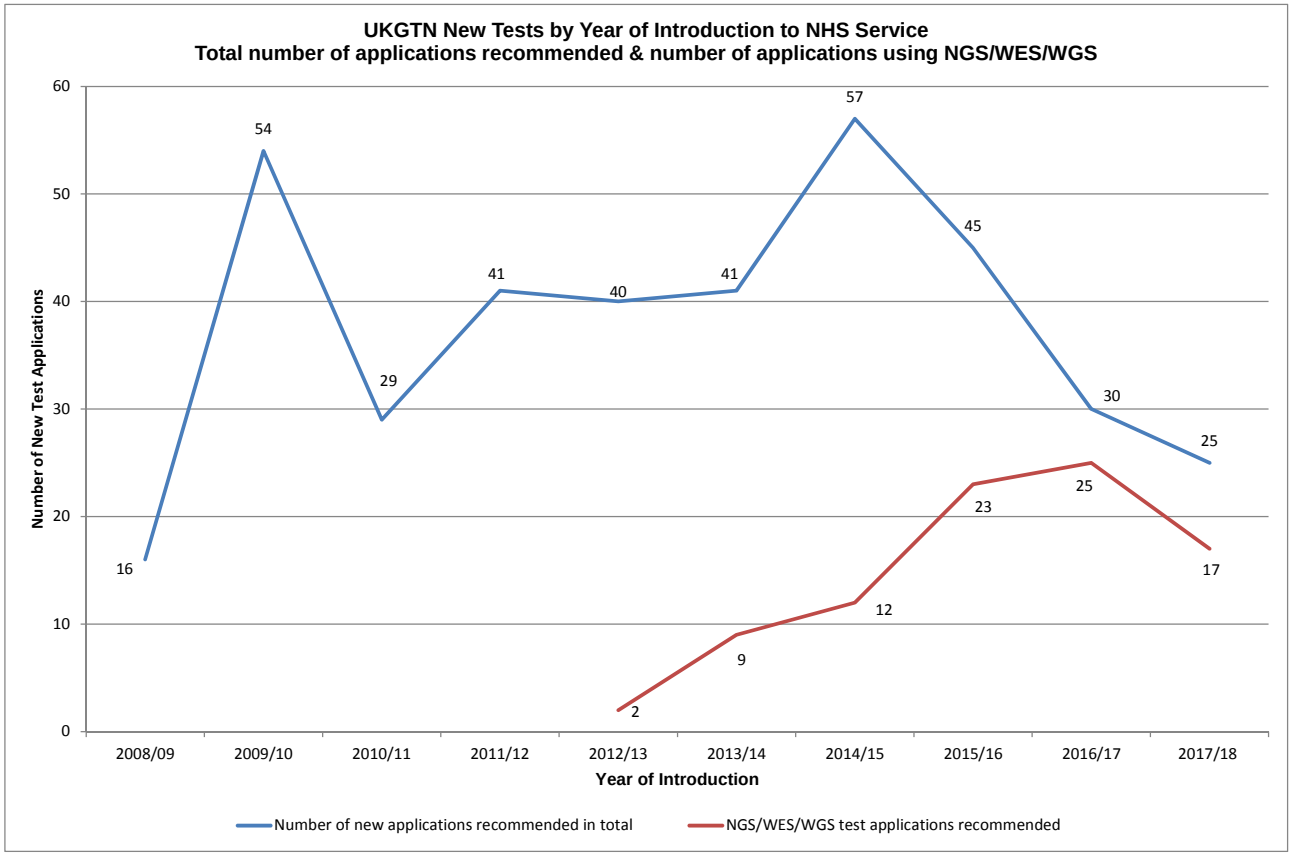
	Home Nation			
	England	**Scotland**	**Northern Ireland**	**Wales**
Investment	£170,791	£16,815	£5,787	£9,723
Savings	£90,824	£8,942	£3,078	£5,170
Net Costs	£79,967	£7,873	£2,709	£4,553

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

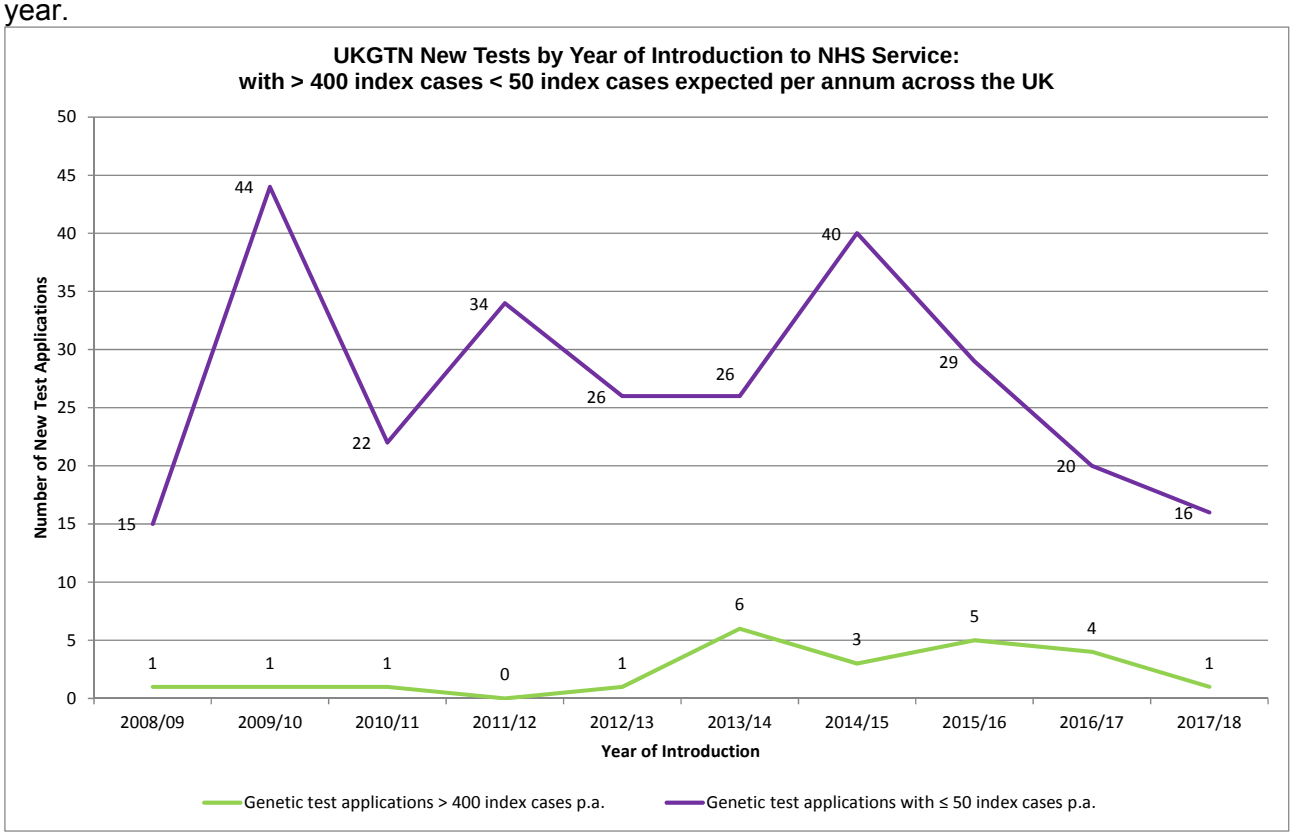
Services to be commissioned from 1st April 2017. The new test service information will be available from the website http://ukgtn.nhs.uk/find-a-test/.

Trend Analysis

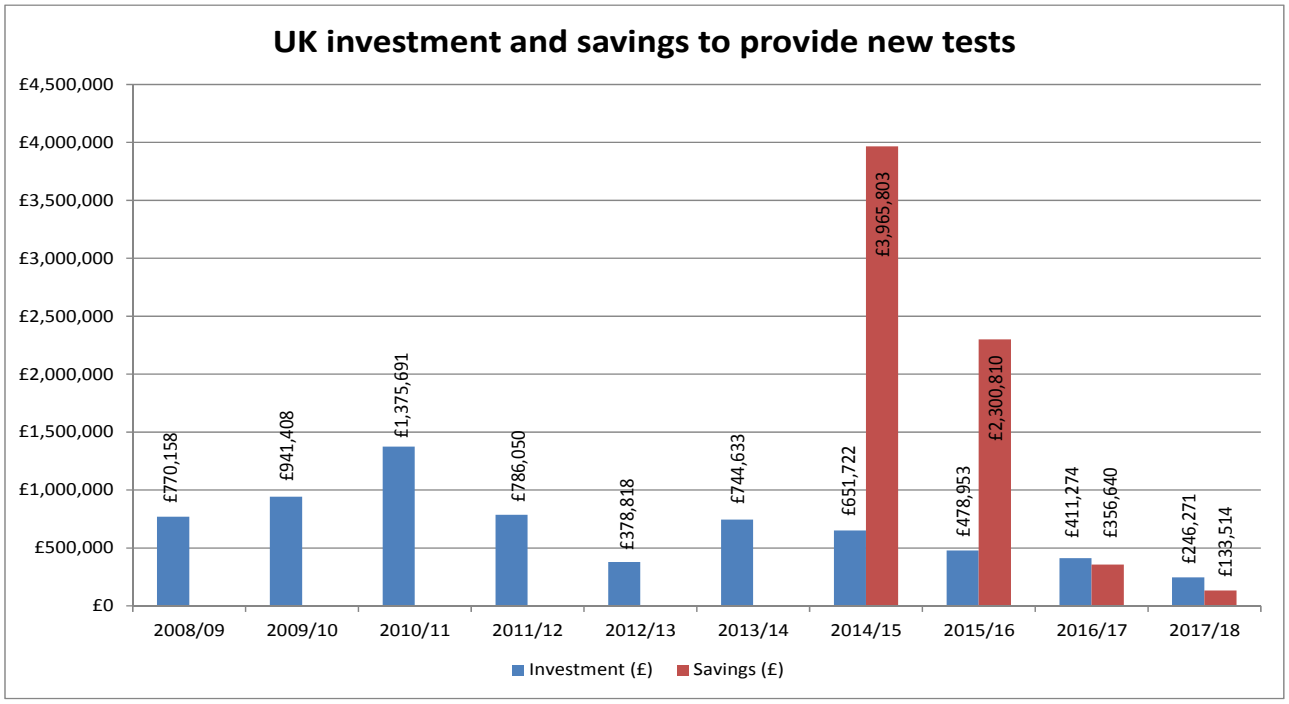
The graph below details the number of new test applications received since 2007 for commissioning from 2008/09. There has been a steady increase in applications over the years followed by a recent decline due in part to an increasing number of large NGS panel test applications.



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

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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 costs based on expected numbers	Estimate of annual costs from clinical genetics	Estimate of annual costs 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
NEW TEST RECOMMENDATIONS TO BE CONSIDERED FOR FUNDING															
#328	Cortical Brain Malformations 43 gene panel	Dr. Andrew Fry	**Cardiff RGC**	£750	£160	100	40	Clinical Geneticists Paediatric Neurologists	E01: Medical Genetics (I=50, F=40) CCG: Neurology, Paediatrics (I=50)	Cost neutral	Cost neutral	Cost neutral	Cost neutral	Cost neutral	Cost neutral
#329	Early Infantile Epileptic Encephalopathy 36 Gene Panel	Professor Angus Clarke	**Cardiff RGC**	£750	£160	150	50	Clinical Geneticists Paediatric Neurologists Adult Neurologists	E01: Medical Genetics (I=75, F=40) CCG: Neurology, Paediatrics (I=65, F=10) CCG: Neurology. Adult (I=10, F=0)	Cost neutral	Cost neutral	Cost neutral	Cost neutral	Cost neutral	Cost neutral
#330	Autoinflammatory Diseases 20 gene panel	Dr Sinisa Savic	**Leeds RGC**	£860	£195	250	50	Clinical Geneticists Paediatric Immunologist Adult Immunologist Paediatric Rheumatologist Adult Rheumatologist	E01: Medical Genetics (I=25, F=25) F06: Specialised Immunology & Allergy Services (Adult and Paediatrics) (I=136, F=16) A09: Specialised Rheumatology (I=21, F=2) E03: Paediatric Medicine (I=68, F=7)	£9,750	£4,875	F06: Specialised Immunology & Allergy Services (Adult & Paeds): £3,120 A09: Specialised Rheumatology: £390 E03: Paediatric Medicine: £1365	£45,000	£4,500	F06: Specialised Immunology & Allergy Services (Adult & Paeds): £24,480 A09: Specialised Rheumatology: £3780 E03: Paediatric Medicine: £12,240
#331	Amelogenesis Imperfecta 21 gene panel	Dr Alan Mighell	**Leeds RGC**	£860	£195	50	33	Clinical Geneticists Specialist or Consultant in Paediatric Dentistry Specialist or Consultant in Restorative Dentistry	E01: Medical Genetics (I=5, F=33) CCG: Paediatric Denistry (I=35, F=0) CCG: Paediatric Dental Surgery (I=10, F=0)	£28,150	£8,607	CCG: Paediatric Denistry £15,200 CCG: Paediatric Dental Surgery £4,343	n/a	n/a	n/a
#332	White Matters Disorders 94 gene panel consisting of 8 sub panels: **Sub panel 1: General** Leukodystrophy & Mitochondrial Leukoencephalopathy 94 gene panel (all genes) **Sub panel 2:** Hypomyelinating Leukodystrophy & Pelizaeus-Merzbacher Disease 12 gene panel **Sub panel 3:** Peroxisome Disorders 14 gene panel **Sub panel 4:** Mitochondrial Leukoencephalopathy 33 gene panel **Sub panel 5:** Leukoencephalopathy with Vanishing White Matter 5 gene panel **Sub panel 6:** X-linked Adrenoleukodystrophy 1 gene panel **Sub panel 7:** Cockayne Syndrome 2 gene panel **Sub panel 8:** Aicardi-Goutieres Syndrome 7 gene panel	John H Livingston	**Leeds RGC**	£860	£170	50	50	Clinical Geneticists Adult Neurologists Paediatric Neurologists Paediatric Metabolic Consultant Adult Metabolic Consultant Paediatrician Neonatologist	E01: Medical Genetics (I=10, F=50) D04: Neurosciences (I=5, F=0) E04: Paediatric Neurosciences (I=25, F=0) E06: Metabolic Disorders (I=4, F=0) E03: Peadiatric Medicine (I=2, F=0) E08: Neonatology Critical Care (I=4, F=0)	£7,000	£7,000	n/a	£63,014	£12,603	D04: Neurosciences £6,301 E04: Paediatric Neurosciences £31,507 E06: Metabolic Disorders £5,041 E03: Peadiatric Medicine £2,521 E08: Neonatology Critical Care £5,041
#333	Perinatal Skeletal Dysplasia & Skeletal Ciliopathy 57 gene panel consisting of 2 sub panels: **Sub panel 1:** Perinatal Skeletal Dysplasia 57 Gene Panel (all genes) **Sub panel 2:** Thoracic and Cranioectodermal Dysplasia (Skeletal Ciliopathy) 15 gene panel	Jennifer Campbell	**Leeds RGC**	£860	£170	40	40	Clinical Geneticists	E01: Medical Genetics (I=40, F=40)	Cost neutral	Cost neutral	Cost neutral	Cost neutral	Cost neutral	Cost neutral
#334 (very rare)	Lateral Meningocele Syndrome	Prof. Peter Turnpenny	**Exeter RGC**	£150	£100	10	5	Clinical Geneticists	E01: Medical Genetics (I=10, F=5)	£2,000	£2,000	n/a	n/a	n/a	n/a
#335	Psuedohypoparathyroidism (Imprinted Methylation Mutations)	Professor Karen Temple	**Salisbury RGC**	£200	£200	50	25	Clinical Geneticists Paediatric Endocrinologists Adult Endocrinologists	E01: Medical Genetics (I=20, F=10) A03: Specialised Endocrinology (I=10, F=5) E03: Paedicatric Medicine (I=20, F=10)	£16,500	£6,600	A03: Specialised Endocrinology £3,300 E03: Paedicatric Medicine £6,600	n/a	n/a	n/a
#336 (#17 and #18 submitted but not approved 01.03.11)	Kallman Syndrome HH1 and HH2	Dr Nicola Foulds	**Salisbury RGC**	£1,000	£175	60	15	Clinical Geneticists Paediatric Endocrinologists Adult Endocrinologists	E01: Medical Genetics (I=10, F=2) A03: Specialised Endocrinology (I=40, F=11) E03: Paedicatric Medicine (I=10, F=2)	£62,625	£10,350	A03: Specialised Endocrinology £41,925 E03: Paedicatric Medicine £10,350	n/a	n/a	n/a
#337	PURA gene sequence analysis	Dr David Hunt	**Salisbury RGC**	£175	£175	100	20	Clinical Geneticists Paediatric Neurologists Neonatologist Paediatrician	E01: Medical Genetics (I=40, F=10) E04: Paediatric Neurosciences (I=30, F=5) E08: Neonatal Critical Care (I=30, F=5)	Cost neutral	Cost neutral	Cost neutral	Cost neutral	Cost neutral	Cost neutral

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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 costs based on expected numbers	Estimate of annual costs from clinical genetics	Estimate of annual costs 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
#339	Neurogenetic Disorders **152** gene panel: Motor Disorders comprising 4 sub panels: **Sub panel 1:** Hereditary Spastic Paraplegia (HSP) **88** gene panel **Sub panel 2:** Familial Amyotrophic Lateral Sclerosis (FALS) with or without Frontotemporal Dementia **42** gene panel **Sub panel 3:** Dementia **27** gene panel **Sub panel 4:** Spinal Muscular Atrophy (SMA) **29** gene panel	Prof Pamala Shaw	**Sheffield RGC**	Sub panels 1, 2 & 4 £975 Sub panel 3 £750	£105	630	190	Clinical Geneticists Paediatric Neurologists Adult Neurologists Psychiatrists	E01: Medical Genetics (I=55, F=130) E04: Paediatric Neurosciences (I=135, F=30) D04: Neurosciences (I=435, F=29) CCG: Psychiatry (I=5, F=1)	For sub panel 4 only £77,091	For sub panel 4 only £16,644	For sub panel 4 only E04: Paediatric Neurosciences £22,777 D04: Neurosciences £37,670	For sub panels 1 - 3 cost neutral For sub panel 4 - no savings	For sub panels 1 - 3 cost neutral For sub panel 4 - no savings	For sub panels 1 - 3 cost neutral For sub panel 4 - no savings
									TOTAL	**£203,116**	**£56,076**	**CRGs: £127,497 CCGs: £19,543**	**£108,014**	**£17,103**	**£90,911**
NEW TESTS NOT RECOMMENDED															
APPLICATIONS EVALUATED IN CYCLE BUT REQUIRE RESUBMISSIONS AND UNABLE TO COMPLETE WITHIN THIS CYCLE															
#338	Hereditary Multiple Osteochondromas 2 Gene Panel		**Salisbury RGC**												
APPLICATIONS SUBMITTED BUT NOT EVALUATED AS TESTS NOT MEETING UKGTN EVALUATION CRITERIA															
#340	Rare Disease service using virtual NGS panels on Clinically Targeted Focused Exome sequencing data (6110 genes)		**Bristol 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												
#328	Cortical Brain Malformations 43 gene panel	**Cardiff RGC**	•		•				•	•	•	•
#329	Early Infantile Epileptic-Encephalopathy 36 Gene Panel	**Cardiff RGC**	•	•	•	•	•	•		•	•	•
#330	Autoinflammatory Diseases 20 gene panel	**Leeds RGC**	•	•	•	•	•	•		•	•	•
#331	Amelogenesis Imperfecta 21 gene panel	**Leeds RGC**	•		•	•	•	•	•	•	•	•
#332	White Matters Disorders 94 gene panel consisting of 8 sub panels:	**Leeds RGC**										
	Sub panel 1: General Leukodystrophy & Mitochondrial Leukoencephalopathy 94 gene panel (all genes)		•	•	•		•		•			•
	Sub panel 2: Hypomyelinating Leukodystrophy & Pelizaeus-Merzbacher Disease 12 gene panel		•	•	•		•		•			•
	Sub panel 3: Peroxisome Disorders 14 gene panel		•	•	•		•		•			•
	Sub panel 4: Mitochondrial Leukoencephalopathy 33 gene panel		•	•	•		•		•			•
	Sub panel 5: Leukoencephalopathy with Vanishing White Matter 5 gene		•	•	•		•		•			•
	Sub panel 6: X-linked Adrenoleukodystrophy 1 gene panel		•	•	•		•		•			•
	Sub panel 7: Cockayne Syndrome 2 gene panel		•	•	•		•		•			•
	Sub panel 8: Aicardi-Goutieres Syndrome 7 gene panel		•	•	•		•		•			•

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)
#333	Perinatal Skeletal Dysplasia & Skeletal Ciliopathy 57 gene panel consisting of 2 sub panels:	**Leeds RGC**										
	Sub panel 1: Perinatal Skeletal Dysplasia 57 Gene Panel (all genes)		•		•	•	•		•	•	•	•
	Sub panel 2: Thoracic and Cranioectodermal Dysplasia (Skeletal Ciliopathy) 15 gene panel		•		•	•	•		•	•	•	•
#334 (very rare)	Lateral Meningocele Syndrome		•		•		•	•	•	•	•	
#335	Psuedohypoparathyroidism (Imprinted Methylation Mutations)		•		•	•	•			•	•	
#336	Kallman Syndrome HH1 and HH2		•		•	•	•	•	•	•	•	
#337	PURA gene sequence analysis		•		•	•			•			
#339	Neurogenetic Disorders **152** gene panel: Motor Disorders comprising 4 sub panels:	**Sheffield RGC**										
	Sub panel 1: Hereditary Spastic Paraplegia (HSP) 88 gene panel		•	•	•	•	•	•	•	•	•	•
	Sub panel 2: Familial Amyotrophic Lateral Sclerosis (FALS) with or without Frontotemporal Dementia 42 gene panel		•	•	•	•	•	•	•	•	•	•
	Sub panel 3: Dementia 27 gene panel		•	•	•	•	•	•	•	•	•	•
	Sub panel 4: Spinal Muscular Atrophy (SMA) 29 gene panel		•	•	•	•	•	•	•	•	•	•

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.