NHS England

CLINICAL PRIORITIES ADVISORY GROUP

Title:

UK Genetic Testing Network (UKGTN) new test recommendations

CPAG is asked to:

Agree the new genetic test recommendations for NHS prescribed specialised services and highly specialised services.

Report Author:

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Governance Clearance:

CRG: ☒ **POC:** ☒ **Finance:** ☐ **Joint CRG/POC Scoring:** ☒

Stakeholder Testing: **Yes** ☐ **No** ☒ **N/A** ☐

No. of stakeholders consulted:

No. of stakeholder responses:

Funding Implications:

Investment: ☒ **Saving:** ☒ **Cost neutral:** ☐

Average cost of care pathway:

No. of Patients to Access/Undergo Procedures per annum:

Total cost:

Details: The UKGTN estimate that cost savings and efficiencies will be realised should the uptake of the genetic tests be in line with the diagnostic care pathways recommended by the expert clinicians. Potential savings are a mixture of actual savings (e.g. NGS replacing Sanger sequencing) and efficiencies as they release capacity for alternative use in the NHS (e.g. MRI no longer required for clinical diagnosis). The savings in medical genetics is due to less index activity and the lower cost of testing family members.

Note: It has not been possible to undertake a test by test financial assurance process and therefore to confirm that the net savings are realisable. At this stage CPAG is therefore asked to consider the investment figure only, as set out below.

Impact on wider commissioning system:

The laboratories require the investment to undertake the tests although the cost savings, if realisable, would be seen within the referring specialty. This will ensure that patients have access to the most up to date and comprehensive genetic testing available.

It is expected that the quantum of genetic testing will continue to rise significantly, circa 18% per annum, in line with genomic diagnostic discoveries which overall could further offset the estimated savings estimated below.

The Genetic Tests on the UKGTN Directory do not include tests for acquired conditions (cancer) or infectious diseases, which are not in the remit of the UKGTN.

Investment required (England only)	**Potential Savings (England only)**
£390,697 for prescribed services of which: £173,670 for medical genetics specialty £206,087 for other specialties **£10,940 for highly specialised services**	**£1,737,810 for prescribed services of which:** £1,020,989 for medical genetics specialty £530,725 for other specialties **£186,096 for highly specialised services**

Executive Summary ⓘ

1. UKGTN was set up by the Department of Health in 2002 to promote genetic testing in the UK. The UKGTN evaluates and makes recommendations on *new genetic tests for NHS service that are provided by UKGTN member laboratories for patients and/or family members with rare conditions.* New genetic tests would not be evaluated by NICE as they fall outside the selection criteria due to their rarity. The UK Strategy for Rare Diseases, building on the CMO Report of 2009, 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.

2. The UKGTN Genetic Test Evaluation Working Group, in the period October 2013 to August 2014:
   - evaluated 48 new test submissions (gene dossiers)
   - recommended 45 new tests of which:
     - 38 are prescribed services and 7 are within Highly Specialised Services

   To note that:
     - 23 are new panel tests that use Next Generation Sequencing
     - 2 are for tests using non-invasive prenatal diagnosis technology

- 11 were evaluated through the very rare disease process (less than 20 index cases a year and less than £5000 annual costs for index cases)

3. Of the new tests recommended 29 are expected to have less than 50 index cases per annum.

4. In addition to clinical genetics specialty, the tests range across:
   - 37 medical specialties
   - 21 Clinical Reference Groups

5. The potential net savings/efficiencies within the care pathway for specialised services for England are £1,347,113 of which:
   - £1,171,957 are released across all CRG prescribed specialised services
   - £175,156 are released from highly specialised services

6. Patient representation and advice to the Genetic Test Evaluation working group is provided from two umbrella groups; Rare Disease UK and Genetic Alliance UK and from three condition specific support groups Mucopolysaccharide Society, CLIMB National Information Centre for Metabolic Diseases and Chronic Granulomatous Disorder Society.

7. Each applicant laboratory submits a Gene Dossier form for each new test to be evaluated. The Gene Dossier provides a standardised format for the evaluation of the key information about a genetic test. A UKGTN multidisciplinary Genetic Test Evaluation working group, including patient representation, performs the evaluation of these applications and one of its key objectives is to confirm the clinical utility of a proposed genetic test. The evaluation process includes both quantitative and qualitative information. The evaluations carried out so far have focused on molecular tests for rare genetic disorders. In many cases the rarity of the conditions results in limited test data and service information being available often including international collaborative material.

8. Every Gene Dossier submitted has to include *Testing Criteria* for the test. *Testing Criteria* defines the key medical features of the genetic disorder and the appropriateness of a genetic test referral. It is intended that the test is only carried out in accordance with the criteria set out in the Gene Dossier and approved by the UKGTN Clinical and Scientific Advisory Group (CSAG). The additional benefit of these criteria is that they are a useful sign post and can inform clinicians' decisions about which investigations are suitable for their patients.

9. The results of the evaluation are reported to the CSAG. Those disorders for which testing has been recommended by the working group and endorsed by the CSAG are recommended to NHS commissioners for funding and added to the NHS Directory of Genetic Disorders/Genes for Diagnostic Testing.

10. The UKGTN has established a process to monitor the approved number of tests performed and will compare these figures to the predicted level of testing. If there is a significant difference then the UKGTN will investigate to establish the reasons for this.

11. CPAG are asked to agree the new genetic tests for NHS service within prescribed services as evaluated through the UKGTN process.

12. Details on each individual genetic test recommended is summarised in the excel spread sheets that are attached:

Attachment 1: Descriptions and Clinical Utility

Attachment 2: Evaluations, costs and savings by CRG – contains 25 spreadsheets; a summary of each test recommended, 21 sheets for each CRG where a test is recommended, 1 sheet for HSS, 1 sheet for CCG services and 1 sheet summarising figures by CRG.

The costs and the savings presented in the summary spread sheet in attachment 2 are calculated for the whole of the UK as these recommendations are considered by all UK countries.The cost savings have been calculated based on the costs of the tests/procedures that are replaced by the genetic test. All approved gene dossiers will be available on the UKGTN website (www.ukgtn.nhs.uk) by December 2014.

13. To link genetic test diagnostic information UKGTN collaborates with Health Education England and the National Laboratory Medicines Catalogue under development by the Royal College of Pathologists.

Jacquie Westwood, UKGTN Director 03.10.14

CLINICAL PRIORITIES ADVISORY GROUP

UK Genetic Testing Network new test recommendations

INTRODUCTION

1. The UKGTN Genetic Test Evaluation Working Group evaluates new genetic tests for NHS service. The evaluation process includes a consideration of the analytical validity, any cost savings in the diagnostic care pathways and the benefits to affected patients and family members.

2. The recommendations contained in this paper to introduce new genetic tests would not be evaluated by NICE as they fall outside the selection criteria.

BACKGROUND

3. The Genetic Test Evaluation process was developed by the UKGTN in association with academic experts in 2003. It is an internationally recognised tool to evaluate genetic tests that once recommended are included on the NHS Directory of Genetic Disorders/Genes for Diagnostic Testing. Once a test is on the Directory it is recommended to be considered for funding through commissioning arrangements. 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 promotes equity, 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/.

CURRENT POSITION

4. The Genetic Test Evaluation Working Group makes recommendations biannually to the governing body of the UKGTN, the Clinical & Scientific Advisory Group (CSAG), when it meets in March and September. The CSAG includes representation from the Royal Colleges and professional bodies and patient groups with input from the Chair of the Medical Genetics Clinical Reference Group. The CSAG endorsed the recommendations for new tests when it met in September 2014. Between 2004-2013 the UKGTN has recommended >350 new tests following evaluation of >440 submissions. A Directory of Genetic Disorders and Genes for Diagnostic Testing lists all the disorders and genes for which there is UKGTN recommended genetic testing. The current version of the Directory, valid as

at March 2014, lists tests for over 1000 disorders that have been subject to evaluation.

The UKGTN NHS Directory of Genetic Disorders/Genes for Diagnostic Testing will continue to grow as a result of the discovery of new disorders and or associated genes. The quantity of the tests recommended is influenced by the changes to technology. Originally the tests offered were for single gene disorders using Sanger sequencing technology. Over the last two years panel tests using next generation sequencing technology have been developed for a number of disorders/genes. Currently the UKGTN directory has 22 Panel tests using next generation sequencing and a further 23 panel tests are recommended in 2014 for service from 2015/16.

A further development of technology allows for next generation sequencing to sequence whole exomes and filtering to analyse specific genes. The UKGTN mechanism allows for evaluation of targeted exome sequencing and a test for primary ciliary dyskineasia has been evaluated using this methodology and is recommended for NHS service. UKGTN is working with its expert advisors to review the mechanisms for evaluating non targeted tests using exome sequencing.

To date very few tests have been removed from the Directory as clinicians make the decision of whether a single gene test or a panel test is appropriate depending on clinical presentation and probability of diagnosis. Currently single gene tests remain clinically relevant depending on the patient presentation. All tests on the Directory are clinically appropriate. All these tests have proven evidence for scientific validity.

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Some previously recommended panel tests are now being extended to include additional conditions and new genes and as a result the previous panel test is withdrawn. To ensure appropriate referrals, panel tests describe the relevant phenotypes and/or the specific related conditions in the testing criteria.

DOES IT WORK?

Severity & Ability of Patients to Benefit

5. The new genetic tests are for a range of rare inherited conditions of which many are severe. A brief description of each condition is included in each gene dossier and summarised on the table listing the genetic tests to be recommended.

6. Each rare disease affects less than 0.1% of our population, but there are >6000 rare diseases of which 4800 are classified. Together they impact on the lives of over 3 million people in the UK.

7. A rare disease is a life-threatening or chronically debilitating disease that affects 5 people or fewer in 10,000, that requires special, combined efforts

to enable patients to be treated effectively. Although the precise number is unknown, the total is steadily rising as new genetic discoveries explain previously unexplained disease patterns. It is estimated that 1 in 17 people will suffer from a rare disease in the course of their lifetime.

8. At least 80% of rare diseases have an identified genetic origin, with 50 per cent of new cases being diagnosed in children.

Clinical Safety & risk

9. Only tests offered by UKGTN member laboratories are evaluated. A condition of membership of the UK Genetic Testing Network is that a laboratory must be accredited by an appropriate body such as Clinical Pathology Accreditation or compliant to ISO17025. As part of this, laboratories will be obliged to participate in external quality assessment schemes for the disorders for which they test or, in the absence of such a scheme, a generic technique based scheme. This requirement provides an assurance to users of the service, patients, clinicians and commissioners, that testing is being carried out to the highest standards.

10. The applications are supported by expert clinicians. These clinicians provide information on the clinical indications when a test would be appropriate. This is summarised in the testing criteria proposed for each test. These criteria also provide guidance on which clinical specialists should refer for each genetic test.

11. The majority of the genetic tests evaluated are low volume and for a significant proportion of applications are for rare diseases. The evidence threshold will therefore vary depending on the population and NHS impact of a proposed genetic test.

12. All the evidence considered in a genetic test application that has been approved is made publicly available on the UKGTN website.

Clinical Effectiveness & Potential for Improving Health

13. The UKGTN has established an evidence based framework for the evaluation of genetic tests. The framework is based on the ACCE (Analytical validity, Clinical validity, Clinical utility, Ethical legal and social implications) which has been validated internationally.

14. For each genetic test application, the analytical validity, clinical validity and clinical utility of the test are evaluated. Test validation and performance data are required. In addition details of the testing pathway and its impact

on the clinical pathway in terms of morbidity and mortality are provided. This includes both positive and negative consequences on the care of the patient and their families. The cost impact is described and alternative testing strategies are considered.

15. The assessment is performed by a multi-disciplinary expert group including clinicians and scientists and patient representatives. The group regularly requests additional data and information as part of its assessment to confirm the performance and benefits of the test under review. In order for a test to be supported, clear and sufficient evidence of the clinical benefits for patients and their families has to be provided.

16. All tests recommended for NHS service improve clinical management and if a familial mutation is found allows for pre natal testing. Specific healthcare outcomes, assessed from the tests recommended, are summarised in the table below:

Healthcare outcome	**Number of tests**
Alerts significant clinical co-morbidities	21
Reduced mortality/saves lives	7
Avoids diagnostic invasive procedures/tests and associated in patient episodes	23
Confirms drug therapy/targeted therapy	31
Earlier diagnosis avoiding multi hospital appointments/procedures	30
Avoids irreversible harm	7
Enables access to educational and social support	6
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	14

DOES IT ADD VALUE TO SOCIETY?

Stimulating Research & Innovation

17. Once a test is approved and included in the UKGTN directory, provision of the service will increase the body of data available to clinical and research

laboratories. However to ensure the maximum benefit is gained from the clinical testing, anonymised data on the mutations and associated phenotypes found in patient samples must be submitted to appropriate, secure databases. Such databases consolidate and extend knowledge of the disease mechanisms for the benefit of patients and in turn contribute to the clinical effectiveness and safety of the test.

Needs of Patient & Society

18. 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. The first invitation to tender to be a NHS England Genomic Medicine Centre was launched in July. It is expected that wave one sites will be announced in early October.

19. 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.

    The four countries have set out implementation plans or statements of intent supporting the 51 commitments in the UK Rare Disease Strategy that was published in December 2013.

IS IT OF REASONABLE COST TO THE PUBLIC?

Average Cost per Patient

20. The average cost per patient for each test is detailed in the summary sheet of each test recommended. It differs depending on the complexity of testing. Of the new tests recommended this year the laboratory costs for testing an affected person range from £100 to just over £1500.

    Overall cost impact and affordability (incl. saving or investment required and impact)

    Table 1: For **all prescribed specialised services** including medical genetics, excluding Highly Specialised Services

Country & Region (England)	POPULATION	INVESTMENT	SAVINGS	NET SAVINGS
England	53,107,169	£379,757	£1,551,714	£1,171,957
North	15,086,775	£107,882	£440,814	£332,932
Midlands and East	16,117,771	£115,254	£470,937	£355,683
London	8,204,407	£58,668	£239,721	£181,053
South	13,698,216	£97,953	£400,242	£302,289

Table 2: For **medical genetics specialised services**, excluding Highly Specialised Services

Country & Region (England)	POPULATION	INVESTMENT	SAVINGS	NET SAVINGS
England	53,107,169	£173,670	£1,020,989	£847,319
North	15,086,775	£49,336	£290,044	£240,708
Midlands and East	16,117,771	£52,708	£309,865	£257,157
London	8,204,407	£26,830	£157,731	£130,900
South	13,698,216	£44,796	£263,349	£218,554

Table 3: For **prescribed specialised services EXCLUDING medical genetics** specialised services and excluding Highly Specialised Services

Country & Region (England)	POPULATION	INVESTMENT	SAVINGS	NET SAVINGS
England	53,107,169	£206,087	£530,725	£324,638
North	15,086,775	£58,546	£150,769	£92,224
Midlands and East	16,117,771	£62,546	£161,072	£98,525
London	8,204,407	£31,838	£81,991	£50,153
South	13,698,216	£53,157	£136,893	£83,736

Table 4: For **Highly Specialised Services** only, excluding all prescribed specialised services

Country & Region (England)	POPULATION	INVESTMENT	SAVINGS	NET SAVINGS
England	53,107,169	£10,940	£186,096	£175,156
North	15,086,775	£3,108	£52,866	£49,759
Midlands and East	16,117,771	£3,320	£56,479	£53,159
London	8,204,407	£1,690	£28,750	£27,059
South	13,698,216	£2,822	£48,001	£45,179

Value for Money Compared to Alternatives

21. In many cases the availability of a genetic test removes the need for other tests/procedures which may be invasive in the diagnostic pathway. This is demonstrated in the gene test evaluations by considering the clinical utility of testing. It is important that new genetic tests that have utility are incorporated into the relevant specialties diagnostic pathways as the savings will usually be in specialties other than clinical genetics. Details of the utility of each test and the potential savings in the diagnostic pathway are provided in the attached Excel spread sheets:

Attachment 1: Descriptions and Clinical Utility

Attachment 2: Evaluations, costs and savings by CRG – contains 25 spreadsheets; a summary of each test recommended, 21 sheets for each CRG where a test is recommended, 1 sheet for HSS, 1 sheet for CCG services and 1 sheet summarising figures by CRG.

IS IT THE BEST WAY OF DELIVERY?

Best Clinical Practice in Delivering the Service?

22. The United Kingdom is a recognised leader in the field of rare disease research, treatment and care. The World Health Assembly resolution in 2010 emphasised the continued significance of rare disorders and the major opportunities for prevention of complications and illness through early diagnosis and action.

23. Currently, the majority of NHS genetics services are delivered by a network of Regional Genetics Centres that offer genetic risk assessment, genetic diagnosis counselling and genetic testing for inherited diseases . They are multidisciplinary, with medical staff

working alongside genetic counsellors, scientists and data handling specialists, and typically serve a regional population of 2–5 million people.

24. In addition, some testing for inherited diseases takes place in other laboratories in pathology, such as biochemistry and haematology (haemoglobinopathies and thrombophilia). These laboratories generally offer both DNA and non-DNA based testing

around a specific specialty. They are also more likely than Regional Genetics Centres to provide testing for acquired genetic mutations (such as cancers).

25. NHSE has recently revised the NHS Genomic Laboratory Service specification for public consultation, prior to a planned procurement. It proposes a national network of Genomic Laboratory services.

Economic Efficiency of Provision

26. New genetic tests will usually allow for some cost savings in the diagnostic pathway and/or savings in regular monitoring of individuals that no longer require follow up and can therefore be discharged from regular surveillance e.g. at risk family members of Sudden Cardiac Death found not to have the familial mutation. The evaluations that are submitted provide case examples both pre and post availability of genetic test to highlight the benefits in patient care, outcomes and costs as demonstrated in this paper.

27. UKGTN promotes the principle that the test is the responsibility of the clinician/hospital that orders the test. The current payment mechanisms for genetic tests vary significantly across England as mapped and reported by UKGTN. This has informed the service specification.

Continuity of Provision

28. There are a limited number of Regional Genetics Centres and associated laboratories. A recent review has led to the publication of a UKGTN Guide to Centres with Specialist Expertise for Rare Genetic Disorders. The Guide demonstrates that 27 laboratories are unique providers of tests for 419 disorders (69%)and that different laboratories have developed specialist expertise in different medical areas. Underpinning the subspecialisation of laboratory services is clinical and/or research expertise that enables a laboratory to provide a cutting edge service for a disorder and the continuity of provision. The Regional Genetic Centres are involved in over 3700 joint specialist clinics providing support to clinical and research teams outside of clinical genetics which is crucial to the laboratories in the development of new services and interpretation of

results. The breadth of services offered indicates that many clinical and laboratory genetic services are integrated into the provision of diagnoses for mainstream medical specialties.

Accessibility & Balanced Geographical Distribution

29. The distribution of genetic testing is reviewed by the UKGTN in reports that provide genetic testing rates by geographical regions based on healthcare organisation boundaries. The report on activity for 2011/12 is available from the UKGTN website http://ukgtn.nhs.uk/our-work/ukgtn-reportsguidelines/ukgtn-molecular-genetic-test-activity-rates-in-the-united-kingdom/ and includes age standardised rates by England Area Teams and Regions and for the equivalent healthcare areas in the devolved countries. Information from the UKGTN on genetic testing rates was included in the national diagnostic themed e-atlas of variation, published in November 2013.

NEXT STEPS

30. This process is undertaken biannually by UKGTN.

RECOMMENDATIONS

CPAG Members are asked to:

- Agree the introduction of the recommended new genetic tests for NHS England commissioned services.

POST DECISION ACTION REQUIRED

UKGTN will:

- Communicate new testing services on UKGTN website
- Evaluate performance of NGS tests post introduction