Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Genetic risk prediction for onset of cardiovascular disease and recurrence of cardiovascular events
Topic exploration report number:	TER218

Introduction and aims

Cardiovascular disease (CVD) includes coronary heart disease (CHD), stroke and peripheral artery disease. These conditions are frequently brought about by the development of atheroma and thrombosis. They are also linked to conditions such as heart failure, chronic kidney disease and dementia. Globally, CVD is the leading cause of death. It is also associated with a large burden of preventable illness.

The current CVD risk assessment pathway in the UK includes clinical assessment for patients at risk of CVD, but not genetic predisposition assessment. GEN inCode is a genetic risk prediction technology based on algorithms and machine learning that combines genetic and clinical data to risk assess patients and provide healthcare professionals with information to evaluate and predict the onset/recurrence of CVD. Patients are then informed of their health risk, enabling them to make lifestyle changes whilst providing clinicians with greater genetic insight and clinical information to determine the most effective treatment pathway. GEN inCode includes six tests; this Topic Exploration Report will focus on the following two tests:

- Cardio inCode: a patented genetic test that analyses genetic variants in DNA related to CVD risk.
- Lipid inCode: a genetic diagnostic test which analyses the seven genes most frequently associated with familial hypercholesterolaemia (FH), which can lead to CVD.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of the above GEN inCode tests and other genetic risk prediction technologies to assess CVD onset/recurrence risk in patients, compared to no genetic risk prediction.

Summary of evidence

Genetic risk prediction technology (GEN inCode) for onset of CVD and recurrence of cardiovascular events is a digital health technology and was determined to be a Tier 3b technology according to the Evidence Standards Framework for Digital Health Technologies**.** This classification covers technologies with measurable user benefits, including tools used for treatment and diagnosis, as well as those influencing clinical management through active monitoring or calculation. For technologies of this classification, it is recommended that high-quality randomised controlled study or studies are produced to demonstrate effectiveness of the technology.

Secondary evidence

Guidance/guidelines

HTW researchers did not identify any guidance or guidelines specific to GEN inCode tests.

The National Institute for Health and Care Excellence (NICE) produced a clinical guideline (CG71) on genetic testing in FH, and stated that an individual with possible or definite FH should receive DNA testing for all gene mutations known to cause FH, and that DNA cascade testing should be undertaken in relatives. An Australian health technology assessment also supported use of genetic testing for FH and based their decision on clinical effectiveness, cost effectiveness and safety.

The European Society of Cardiology states that whilst genetic screening and counselling is effective in some conditions, such as FH, it does not recommend use of DNA-based tests for cardiovascular risk assessment in the general population. The American Heart Association provided a scientific statement, which summarises the best practices with respect to genetic testing and its implications for the management of inherited CVD.

Systematic reviews

We did not find any systematic reviews looking specifically at GEN inCode tests. We identified five recent meta-analyses (since 2019) that suggested a genetic link to cardiovascular events, but did not mention GEN inCode. These are described in the Brief Literature Results section.

One meta-analysis found no clear evidence that genetic-risk communication alone either raises motivation or translates into actual change in dietary intake or physical activity to reduce the risk of cardiometabolic disorders in adults (Li et al. 2016).

Economic evaluations

We identified one economic evaluation for the Cardio inCode test. We did not identify any economic evidence for the Lipid inCode test. The manufacturer stated that the cost of GEN inCode tests is primarily related to the cost of the genetic test, algorithmic processing and patient reporting.

In an economic analysis, by Ramirez de Arellano et al. 2013, patients classified as high-risk using Cardio inCode were assumed to receive statins and antihypertensive medication, which reduced the risk of coronary disease by 24.4% in Year 1, 53.3% in Year 2, 73.3% in Year 3, and 80% per year thereafter. The reduction in events lead to quality-adjusted life-year (QALY) benefits and cost savings but the cost savings weren't high enough to make it cost saving overall. It was, however, found to be cost effective, with an incremental cost-effectiveness ratio (ICER) of around £13,000 per QALY.

NICE CG71 reported that DNA-based testing methods for cascade screening of FH were more cost-effective when compared to the cholesterol-testing method, with an estimated incremental cost-effectiveness ratio (ICER) of £2,676 per QALY. The model results were stable in sensitivity analysis.

Primary studies

Prediction of cardiovascular events

The manufacturer informed us of numerous case-control and cohort studies evaluating GEN inCode tests in the prediction of cardiovascular events. These references are provided in the Brief Literature Results section.

- Cardio inCode

The Topic Proposer informed us of five cohort and case-control studies, ranging from 81 to 51,954 participants, which suggest that the genetic risk score of Cardio inCode is associated with the risk of presenting a coronary accident.

- Lipid inCode

Amor-Salamanca (2017) conducted a cohort study which showed that approximately 9% of a group of 103 patients with acute coronary syndrome presented a FH pathology (DNA sequencing was performed with Lipid inCode).

Other outcomes

Health Technology Wales researchers did not identify any studies reporting outcomes regarding the impact genetic risk prediction tests have on the CVD management of patients and their family members (e.g. lipid-lowering treatment rates, surgical intervention rates, number of cardiovascular events, mortality, screening for other abnormalities).

Ongoing research

We did not identify any ongoing studies of clinical or cost effectiveness of genetic risk prediction technologies for CVD onset/recurrence.

Areas of uncertainty

The majority of the evidence was for onset of CVD and not recurrence: further studies investigating the tests for recurrent CVD would be beneficial. In addition, the cost effectiveness of Lipid inCode could not be determined.

It was difficult to identify the genetic risk prediction tests used in the systematic reviews, and whether the genes analysed were the same as the ones looked at by GEN inCode. Further scrutiny of the evidence would be needed to determine this.

There is uncertainty as to whether genetic risk prediction for CVD will change the behaviour of people at risk of CVD.

Conclusions

Observational studies identified for GEN inCode tests suggest they can predict risk of cardiovascular events, but their effect on downstream outcomes, such as better management of cardiovascular disease or a reduction in cardiovascular events, is unclear based on the evidence identified.

An economic evaluation for one of the two GEN inCode tests found it to be cost effective. The majority of the clinical evidence we found was for genetic risk prediction in onset of CVD. Guidance exists for use of genetic tests in FH, and meta-analyses evaluating the genetic link to cardiovascular events were identified. However, the meta-analyses were not associated with GEN inCode tests specifically and further scrutiny of them is needed.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant evidence from this source
Health Technology Assessment Group	We did not identify any relevant evidence from this source
Health Information and Quality Authority	We did not identify any relevant evidence from this source
EUnetHTA	We did not identify any relevant evidence from this source
International HTA Database	Australian Government. Medical Services Advisory Committee. Adelaide Health Technology Assessment. 2019. Heritable mutations associated with Familial Hypercholesterolaemia: https://database.inahta.org/article/18601
UK guidelines and guidance	
SIGN	We did not identify any relevant evidence from this source
NICE	Clinical guideline (CG71). Familial hypercholesterolaemia: identification and management. October 2019: https://www.nice.org.uk/guidance/cg71 CG71. 2008. Appendix E. Health economic modelling: https://www.nice.org.uk/guidance/cg71/evidence
International guidelines and guidance	
European Society of Cardiology	CVD prevention in clinical practice (European guidelines on) guidelines. 2016. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Rendon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S, ESC Scientific Document Group. European Heart Journal: 37 (29): https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/CVD-Prevention-in-clinical-practice-European-Guidelines-on
American Heart Association	Musunuru K, Hershberger RE, Day SM, Klinedinst NJ et al. 2020. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. Circulation: Genomic and Precision Medicine; 13(4): https://www.ahajournals.org/doi/epub/10.1161/HCG.0000000000000067
Secondary literature and economic evaluations	
https://www.tripdatabase.com/	Ramirez de Arellano A, Coca A, de la Figuera M, Rubio-Terres C, Rubio- Rodriguez D, Gracia A, Boldeanu A, Puig-Gilberte J, Salas E. 2013. Economic evaluation of Cardio inCode(R), a clinical-genetic function for coronary heart disease risk assessment. Applied Health Economics and Health Policy;11: 531–542.: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3825137/

Cochrane library	No additional relevant evidence identified.
Medline (via Ovid or Pubmed)	Lee S, Akioyamen LE, Aljenedil S, Rivière JB, Ruel I, Genest J. 2019. Genetic testing for familial hypercholesterolemia: impact on diagnosis, treatment and cardiovascular risk. European Journal of Preventive Cardiology; 26(12): https://doi.org/10.1177/2047487319829746 *Study found that the lifetime risk of atherosclerotic CVD is 4.4- to 6.8-fold increased in patients with a FH-causing variant compared with controls.* Li Y, Yuan H, Sun L, Zhou Q, Yang F, Yang Z, Liu D. 2019. ß2-Adrenergic Receptor Gene Polymorphisms Are Associated with Cardiovascular Events But not All-Cause Mortality in Coronary Artery Disease Patients: A Meta-Analysis of Prospective Studies. Genetic Testing and Molecular Biomarkers; 23(2): 124-137: doi: 10.1089/gtmb.2018.0153. *Study found that patients harbouring the ADRB2 rs1042714 allele presented a positive association with cardiovascular events but not with all-cause mortality in CAD patients* Li SX, Ye Z, Whelan K, Truby H. 2016. The effect of communicating the genetic risk of cardiometabolic disorders on motivation and actual engagement in preventative lifestyle modification and clinical outcome: a systematic review and meta-analysis of randomised controlled trials. The British Journal of Nutrition; 116(5): 924-934: doi: 10.1017/S0007114516002488 Lu S, Zhong J, Huang K, Zhou H. 2019. Association of IL-10-1082A/G polymorphism with cardiovascular disease risk: Evidence from a case–control study to an updated meta-analysis. Molecular Genetics and Genomic Medicine; 7(11): https://doi.org/10.1002/mgg3.888 *Meta-analysis proposed that the IL-10 polymorphism may serve as a risk factor for CVDs.* Xu JJ, Liu KQ, Ying ZM, XW Zhu, XJ Xu, PP Zhao, Bai WY, Qiu MC, XW Zhang, Zheng HF. 2019. Effect of CD14 polymorphisms on the risk of cardiovascular disease: evidence from a meta-analysis. Lipids in Health and Disease; 18(74): https://lipidworld.biomedcentral.com/articles/10.1186/s12944-019-1018-3 *Meta-analysis concluded that the CD14 gene single nucleotide polymorphism rs2569190 significantly contributed to susceptibility and development of CVD, particularly in the East Asian population.* Zhai CN, Cong HL, Zhang H, Hou K, Zhang Y, Zhang YY. 2019. M235T polymorphism in the angiotensinogen gene and cardiovascular disease: an updated meta-analysis of 39 case-control comparisons. The Anatolian Journal of Cardiology; 21(4): 222-232:

	doi: 10.14744/AnatolJCardiol.2019.75282 *This meta-analysis suggested that the angiotensinogen gene variant M235T is associated with CVD risk in the Asian population.*
Primary studies	
https://www.epistemonikos.org/en/	No additional relevant evidence identified
https://www.tripdatabase.com/	
Cochrane library	
Medline	
Ongoing primary or secondary research	
PROSPERO database	No additional relevant evidence identified
Clinicaltrials.gov	
Other	
Evidence provided by the topic proposer	• *Cardio inCode* Iribarren C, Lu M, Jorgenson E, Martínez M, Lluis-Ganella C, Subirana I, Salas E, Elosua R. 2016. Clinical utility of multimarker genetic risk scores for prediction of incident heart disease. A cohort study among over 51000 individuals of European ancestry. Circulation, Cardiovascular Genetics; 9: 531-540: DOI: 10.1161/CIRCGENETICS.116.001522 Iribarren C, Lu M, Jorgenson E, Martínez M, Lluis-Ganella C, Subirana I, Salas E, Elosua R. 2018. Weighted multi-marker genetic risk scores for incident coronary heart disease among individuals of African, Latino and East-Asian Ancestry. Circulation, Cardiovascular Genetics; 8(1): 6853: DOI: 10.1038/s41598-018-25128-x Lluis-Ganella C, Lucas G, Subirana I, Senti M, Jiminez-Conde J, Marrugat J, Tomás M, Elosua R. 2010. Additive effects of multiple genetic variants on the risk of coronary artery disease. Revista Española de Cardiología (English Edition); 63(8): 925-33: DOI: 10.1016/s1885-5857(10)70186-9 Lluis-Ganella C, Subirana I, Lucas G, Tomás M, Muñoz D, Senti M, Salas E, Sala J, Ramos R, Ordovas JM, Marrugat J, Elosua. 2012. Assessment of the value of a genetic risk score in improving the estimation of coronary risk. Atherosclerosis; 222: 456-463: doi: 10.1016/j.atherosclerosis.2012.03.024 Rincón LM, Sanmartín M, Alonso JA, Muriel A, Casas E, Navarro M, Carbonell A, Lázaro C, Fernández S, González P, Rodríguez M, Jiménez-Mena M, Fernández-Golfin C, Esteban A, García-Bermejo ML, Zamorano JL.

	2020. A genetic risk score predicts recurrent events after myocardial infarction in young adults. Revista Española de Cardiología (English Edition); Revista Española de Cardiología (English Edition); 73(8): 623 – 631: https://doi.org/10.1016/j.rec.2019.08.006 • *Lipid inCode* Amor-Salamanca A, Castillo S, Gonzalez-Vioque E, Dominguez F, Quintana L, Lluís-Ganella C, Escudier JM, Ortega J, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. 2017. Genetically Confirmed Familial Hypercholesterolemia in Patients With Acute Coronary Syndrome. Journal of the American College of Cardiology; 70(14): 1732-1740*:* https://doi.org/10.1016/j.jacc.2017.08.009

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Concepts used:	inCode, genetic, DNA, risk, cardiovascular, CVD, genetic risk prediction