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A feasibility study of whole genome germline testing as an adjunct screening tool in a UK general private practice

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Whole genome sequencing (WGS) presents an opportunity to identify asymptomatic individuals at increased risk for disease. We set up a model pathway to assess the use of WGS combined with a medical assessment in primary care. We recruited 104 participants (102 unrelated) from a private general practice for a medical assessment, WGS and panel testing. WGS analysed 566 clinically actionable genes, including moderate to high-risk monogenic traits, recessive traits and pharmacogenes. Polygenic risk scores (PRS) were calculated for 4 cancers. Twenty-three individuals (22%) had an actionable germline variant in cancer, cardiac, lipid or thromboembolic genes. Ten of these (43%) had pathogenic variants in cancer predisposition genes, 60 (58%) participants harboured recessive genetic alterations and 43 (41%) had pharmacogenetic variants. Our findings show WGS in primary care identified actionable variants in 22% of individuals resulting in a change in clinical management. Pharmacogenomics may alter prescribing in a further 41%.

Whole genome sequencing (WGS) is now possible due to improvements in next generation sequencing technology.

There is considerable interest in this area by the Department of Health through the Genomes England initiative (https://www.genomicsengland.co.uk) which aims to integrate genomics into healthcare. This remit was highlighted in Genome UK, The Future of Healthcare 2020[1]. Recommendations include that 'the National Screening Committee conducts a systematic evaluation of opportunities offered by genomics for present and potential screening practices', at national, population-based, or individual levels. With the advent of the NHS Genomic Medicine Service[2] and subsequent implementation of The Generation Study (https://www.genomicsengland.co.uk/initiatives/newborns), integrating DNA screening into routine healthcare is becoming a reality. It is anticipated that genomic testing rates will double in the next five years[3] and how testing is implemented in the primary care setting will be central.

Studies have shown that genomic analyses of tumour and germline DNA alter clinical care e.g[4,5]. The 100,000 Genomes Project demonstrated the utility of WGS technology as it led to a new diagnosis for up to a quarter of patients tested for rare diseases, cancer, and infections[6]. A proportion of diagnoses were made using genome wide data.

Research has also assessed the integration of genomic medicine in primary care and community settings in the United States (US) by detecting disease-risk alleles and pharmacogenomic variants[7–9].

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Large population-based initiatives are underway using WGS or genotyping arrays in the US and UK (https://www.researchallofus.org and https://ourfuturehealth.org.uk) using larger, more diverse genetic research resources on a voluntary basis to inform healthcare.

The role of WGS in primary care in the UK has not yet been reported. This paper reports the development of a genomics-integrated model care pathway that incorporates the complex interpretations of WGS data into primary care.

Results

106 participants were recruited between December 2019 and July 2022. After exclusions, (one participant withdrew and one had active cancer at the time of WGS testing), 104 (102 unrelated) participants were included in the final analysis. Fourteen participants had a previous cancer diagnosis. None of the participants were found to have a previous history of inherited cardiomyopathy or cardiac arrhythmia. Median age at study entry was 59.5 years (range: 30–83), and 63% were male. Most participants (95.2%) were of self-reported European ancestry. More than 75% reported a positive family history of cancer or cardiac disease in a first or second-degree relative (Table 1).

Actionable genetic variants

WGS and clinical gene panel testing detected 23 participants (22%) with actionable genetic variants among fifteen genes and eighteen unique LP/P variants. Table 2 lists the detected clinically actionable variants found in each participant. A total of 22 individuals had a variant that led to a recommended change in management.

For these individuals, enhanced investigations, screening and/or risk-reducing surgery was recommended. Cascade testing in the families was recommended to facilitate disease prevention in at-risk relatives.

Of the ten cancer predisposition gene (CPG) variants detected, 6 (60%) would not have been identified using UK National Genomic Test Directory (NGTD) testing guidelines. This highlights an added benefit of implementing WGS screening programme among CPGs, demonstrating a 60% increased genetic diagnostic yield. In contrast, if this programme were based in the US, the genetic diagnostic yield would be 30% (3/10), reflecting differences in testing criteria, healthcare funding and resource allocation. Two first-degree relatives of Ashkenazi ancestry were found to have the *APC* p.I1307K variant; one of which had colon cancer diagnosed at < 30 years of age. The penetrance of this susceptibility variant is known to be variable, and interpretation of *APC* associated risk estimates[10] depend on family history of the associated condition, hence their inclusion.

Two individuals were found to carry pathogenic variants in *SDHA*, neither of whom had a family history of *SDHA*-related cancers. The estimated penetrance of *SDHA* variants ascertained in this context is < 5%, such that, in the public sector they would not be offered screening for SDHA-associated tumours according to the UK guidelines[11]. One individual was found to have a low penetrance *FH* variant, which is important for family planning, but associated risk of renal cancer in heterozygous state is uncertain[12]. However, in our study these individuals were both offered on-going surveillance, and cascade testing was offered to at-risk family members. If the *APC* and *SDHA* variants are excluded, then the incidence of actionable cancer associated variants is 19%.

No LP/P gene variants associated with cardiomyopathies or aortopathies were detected in this cohort. Three individuals were found to have a LP variant in *KCNE1* that could impact prescribing, while three had P variants conferring increased risk of hyperlipidaemia, which would alter dietetic and pharmacological management.

A compound heterozygous P variant was detected in an individual with a first degree relative known to have haemochromatosis. Two individuals were found to be homozygous for the *HFE* variant p.C282Y, one of which had a diagnosis of haemochromatosis a priori. We recommended cascade testing for the p.C282Y variant in at-risk relatives[13]. We excluded the low penetrance common p.H63D variant in *HFE* from the actionable variant list as this variant is rarely associated with iron overload, even in the homozygous state[14].

	Individuals tested with WGS (*N* = 104)
Median Age [range]	59.5 [30–83]
	n (%)
Male	66/104 (63%)
Ethnicity European ancestry Non-European ancestry	 99/104 (95.2%) 5/104 (4.8%)
Personal history of cancer prior to genetic testing Yes No	 14/104 (13.5%) 90/104 (86.5%)
Family history of cancer* (Any cancer reported in 1 st or 2nd degree relative) Yes No	 76/103[+] (73.8%) 27/103 (26.2%)
Previous thrombotic event Yes No	 4/104 (3.8%) 100/104 (96.2%)
Previous iron metabolism abnormality Yes No	1/104 (0.96%) 103/104 (99.04%)

Table 1. Descriptive characteristics for individuals receiving WGS testing. *Defined as a preexisting condition or event known before WGS testing. [+]One individual did not complete family history questionnaire.

LP/*P* Actionable variant(s) detected with WGS	Past Medical History of relevant condition (Affected/Unaffected)	Family History of Cancer* (tumour type)	Management change(s)	Eligible for genetic testing as per NHS England NGTD	Eligible for genetic testing as per NCCN guidelines
40-year-old female *SDHA* c.1534 C > T (p.Arg512*) heterozygote *DPYD* C.1905 + 1G > A; heterozygote	Unaffected	Yes (Breast, stomach)	Baseline MRI, consider biochemical screening, refer to Endocrinologist Relevant if treatment with 5FU required	No	No
56-year-old female *BARD1* c.2148_2149del (p.Ile717Glnfs*12) heterozygote	Unaffected	Yes (Breast < 50, prostate)	Patient preference to proceed with prophylactic salpingo- oophorectomy; aware that reported associated risk does not reach threshold at which this would ordinarily be recommended. For 2 yearly breast screening (as per standard in the private sector)	No	No
53-year-old male *BRCA1* c.3351dupT (p.Gln1118serfs*4) heterozygote	Unaffected	Yes (Breast, ovarian)	Annual PSA from age 40	Yes	Yes
71-year-old female *PALB2* c.1059_1077delinsGG (p.Ser354Glyfs*4) heterozygote	Affected (bladder cancer prior to WGS test)	Yes (Kidney, breast, prostate)	For high-risk breast surveillance or RRS; RR BSO optional	Yes	Yes
63-year-old male *APC* c.3920T > A (p.Ile1307Lys) heterozygote	Affected (colon cancer age 29)	No	MDT decision to continue annual colonoscopies due to early age of onset*	No	Yes
73-year-old female *APC** c.3920T > A (p.Ile1307Lys) heterozygote	Unaffected	Yes (Colon; sibling of other *APC* carrier)	MDT decision to start three yearly colonoscopy screening	No	Yes
55-year-old female *SDHA* c.91 C > T (p.Arg31*) heterozygote *APOE* e2/e2 homozygote	Unaffected	Yes (Prostate, breast, ovarian)	Baseline MRI, consider biochemical screening, refer to Endocrinologist, Lipid monitoring, CT coronary angiogram, carotid doppler, diet and exercise advice	No	No
42-year-old male *MSH2* c.1225 C > T (p.Gln409*) heterozygote	Affected (previous testicular and colon cancer < 50)	No	Annual colonoscopy: advised to start aspirin 300 mg od; renal tract imaging (as part of previous cancer follow-up) and upper GI endoscopy; prostate screening as per IMPACT study. Lynch registry.	Yes	Yes
50-year-old male *MSH6* c.742 C > T (p.Arg248*) heterozygote	Unaffected	Yes (Lymphoma, squamous cell carcinoma skin)	Two yearly colonoscopy surveillance unless polyps seen; Discuss daily prophylactic Aspirin 150-300 mg; Prostate screening as per IMPACT study; Lynch registry	Yes	Yes
42-year-old male *FH* c.1431_1433dup (p.Lys477dup) LP heterozygote	Unaffected	Yes (Bowel < 50)	Consensus at present is that cancer risk in heterozygotes likely to be low Both kidneys normal on recent abdominal USS. Implications for family planning.	No	Yes
46-year-old female *F5* c.1601G > A (p.Arg534Gln) heterozygote	Unaffected	Yes (Sigmoid colon < 50)	VTE prophylactic advice	N/A	N/A
63-year-old male *F5* c.1601G > A (p.Arg534Gln) heterozygote	Jan 2022 newly diagnosed with prostate cancer via PSA, MRI screening and subsequent biopsy	Yes (Bowel)	VTE prophylactic advice	N/A	N/A
40-year-old female *LDLR* c.1247G > A (p.Arg416Gln) heterozygote	Unaffected LDL 2.9 mmol/L	Yes (Prostate, colon)	Advice regarding modifiable risk factors, annual cholesterol check.	N/A	N/A
58-year-old female *F2* c.*97G > A Het (Non-coding) low penetrance heterozygote *DPYD* c.2846 A > T (p.Asp949Val) heterozygote	Unaffected	Yes (Breast < 50., prostate)	VTE prophylactic advice Relevant if treatment with 5FU required	N/A	N/A
72-year-old male *F2* c.*97G > A Het (Non-coding) low penetrance heterozygote	Unaffected at time of genetic testing; subsequently dx prostate cancer; (ECG LBBB & Echo apical inferior hypokinesia)	Yes (Prostate, breast)	VTE prophylactic advice, CTCA	N/A	N/A
52-year-old female *F2* c.*97G > A Het (Non-coding) low penetrance heterozygote	Unaffected (Previous breast cancer)	Yes (Prostate)	VTE prophylactic advice	N/A	N/A
44-year-old male *F2* c.*97G > A Het (Non-coding) low penetrance heterozygote	Unaffected	Yes (Prostate)	VTE prophylactic advice	N/A	N/A
74-year-old female *KCNE1* c.253G > A (p.Asp85Asn) LP heterozygote	Unaffected (Breast cancer 2013)	No	Avoid QT prolonging drugs	N/A	N/A
77-year-old female *KCNE1* c.253G > A (p.Asp85Asn) LP heterozygote	Unaffected	Yes (Ovarian, liposarcoma)	Avoid QT prolonging drugs	N/A	N/A

Continued

LP/*P* Actionable variant(s) detected with WGS	Past Medical History of relevant condition (Affected/Unaffected)	Family History of Cancer* (tumour type)	Management change(s)	Eligible for genetic testing as per NHS England NGTD	Eligible for genetic testing as per NCCN guidelines
74-year-old male *KCNE1* c.253G > A (p.Asp85Asn) LP heterozygote *HFE* c.845G > A (p.Cys282Tyr) homozygote	Known diagnosis haemochromatosis and previous venesection	No	Avoid QT prolonging drugs Annual iron indices	N/A	N/A
68-year-old male *HFE* c.845G > A (p.Cys282Tyr) homozygote *DPYD* c.1905 + 1G > A heterozygote	Unaffected Atrial fibrillation, HTN; normal iron indices	Yes (Breast, lung)	Annual iron indices; Annual blood tests for HFE Relevant if treatment with 5FU required	N/A	N/A
37-year-old female *HFE* c.845G > A (p.His63Asp(;)(p.Cys282Tyr) compound heterozygote	Unaffected normal iron indices Father known to have haemochromatosis	Yes (Liver and bowel)	Review bloods after menopause; cascade testing	N/A	N/A
66-year-old male *APOE* e2/e2 homozygote	Unaffected	Yes (Prostate)	Lipid monitoring, CTCA, carotid doppler, diet and exercise advice	N/A	N/A

Table 2. Change(s) in patient management following detection of actionable variants using WGS. *This individual continued with the same management as detection of the variant did not change the screening interval; therefore, this case was excluded the calculation of number of variants that change management. NGTD- NHS England National Genomic Test Directory. NCCN – National Comprehensive Cancer Network USA. PSA – prostate specific antigen. RRS- risk reducing surgery; RRBSO – risk reducing bilateral salpingo-oophorectomy. VTE -venous thromboembolism. IMPACT – Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in men at higher genetic risk and controls. CTCA – CT coronary angiogram. All actionable variants were considered for cascade testing.

There was no difference in the detection of LP/P variants on the panel tests and the WGS. Panel tests showed that 50% of the cohort had at least one VUS.

Carrier genes

At present, testing partners of carriers of recessive variants in the relevant gene is offered if the carrier frequency is at least 1 in 70, if the patient is in a consanguineous relationship or their partner has a relevant family history. Recessive genetic alterations were identified in 58% (60/104) of individuals in this study, but carrier frequency was lower than the current threshold for NHS-funded partner testing in a quarter of these cases. The associated recessive disorders ranged from a relatively mild or adult-onset disorder, to severe, life limiting, childhood or neonatal onset conditions e.g. Tay Sachs. Table 3 lists the carrier variants detected within the cohort.

Pharmacogenomics

Table 4 shows the number of pharmacogenetic variants detected in the cohort. Overall, 41% of participants had clinically actionable variants: 39 in *CYP2C19* impacting the metabolism of Clopidogrel and 4 *DPYD* variants affecting fluoropyrimidine/capecitabine metabolism. This would necessitate a change in management (dose adjustment or alternative drug) if these medications were required or already prescribed.

30% of participants (32/104) were found to carry a variant in *SLCO1B1* which may impact statin metabolism. 20% (21/104) of participants carried a variant in *CYP2D6* that affects metabolism of analgesics such as Codeine; and 19% (20/104) had a variant in *VKCORC1* affecting vitamin K – related anticoagulant metabolism. These were assessed using CPIC pharmacogenomic guidelines[15,16]. The guidelines classify 20 genes that have strong evidence for gene-drug interactions and recommend their inclusion when performing pharmacogenomic analysis. As part of this study, WGS output was examined for variants in 15/20 recommended genes. Genes that were not interrogated included *HLA-A*, *HLA-B*, *IFNL3*, *IFNL4*, and *MT-RNR1*.

Results of the medical assessments

One-third of participants (34/104) had a new diagnosis and/or change of management because of the medical assessment (Supplementary Table 1). None of these individuals were found to have a LP/P variant that influenced management. Two patients were found to have more than one medical finding necessitating further investigations. Echocardiogram and abdominopelvic ultrasound resulted in a change of management in 62% and 12% of individuals respectively. Medical assessments found 31 incidental medical findings on imaging (see Supplementary Table 2).

Polygenic risk scores (PRS)

The availability of WGS data enabled analysis of PRS score which was calculated for four cancers (prostate, breast, colon, and ovary). Results were fed back as research results to participants, and they were offered enrolment to research screening studies as appropriate. The results are shown in in Fig. 1a-d. All individuals who were either previously or subsequently diagnosed with cancer are marked.

Discussion

As genomic medicine continues to advance, genomic testing will reshape how healthcare systems approach preventive and personalised medicine. Primary care is the central hub of holistic healthcare. Our report is the first of its kind in the UK to look at WGS as an adjunct to health screening in primary care using a model

Gene	Variant
TRMU	c.718 C > T (p.Arg240*)
EYS *BBS1*	c.2137 + 1G > A (p.?) c.1169T > G (p.Met390Arg)
GALT *PEX6*	c.−67-52_−67-49delGTCA c.1802G > A (p.Arg601Gln)
GALT *SCO2*	c.67 − 52_−67 49delGTCA c.157 C > T (p.Gln53*)
FAH *PMM2*	c.1021 C > T(p.Arg341Trp) c.470T > C (p.Phe157Ser)
BCHE	c.812 C > T (p.Thr271Met)
G6PC *HEXA*	c.247 C > T (p.Arg83Cys) c.1274_1277dupTATC (p.Tyr427Ilefs*5)
CFTR *TYR*	c.1624G > T (p.Gly542*) c.1217 C > T (p.Pro406Leu)
PAH *GALT*	c.1066–3 C > T c.−67-52_−67-49delGTCA
CYP1B1 *CFTR* *SLC12A3*	c.1159G > A (p.Glu387Lys) c.1210-34TG[11]T[5] c.2221G > A (p.Gly741Arg)
SLC25A13	c.1487delT (p.Phe496Serfs*12)
B4GALT7 *GALT*	c.1003T > C (p.Phe335Leu) c.−67-52_−67-49delGTCA
SLC26A4	c.1003T > C (p.Phe335Leu)
POLG	c.2243G > C (p.Trp748Ser)
GJB2	c.416G > A (p.Ser139Asn)
TYR	c.1217 C > T (p.Pro406Leu)
ARSA *SERPINA1*	c.465 + 1G > A c.739 C > T (p.Arg247Cys) [F allele]
PEX6	c.1802G > A (p.Arg601Gln)
PMM2	c.422G > A (p.Arg141His)
LAMA2 *TPP1* *BCHE*	c.7658delC (p.Ser2553Tyrs*54) c.509-1G > C c.293 A > G (p.Asp98Gly)
MPL *BCHE*	c.305G > C (p.Arg102Pro) c.293 A > G (Asp98Gly)
CFTR	c.1210-34TG[11]T[5]
LIPA *SERAPINA*	c.894G > A (p.Gln298=) Pi*MS
RYR1 *TSHR*	c.13525_13531dupGGGGAGA c.1637G > A
GALT	c.−67-52_−67-49delGTCA
FAH	c.1021 C > T (p.Arg341Trp)
TSHR *SLC22A5*	c.1228G > A (p.Asp410Asn) c.364G > T (p.Asp122Tyr)
GALT *F11*	c.−67-52_−67-49delGTCA c.403G > T (p.Glu135*)
FAH	c.1021 C > T (p.Arg341Trp)
BBS1	c.1169T > G (p.Met390Arg
DIS3L2 gain(Exon 8) *ALDOB*	CN = 3 c.448G > C (p.Ala150Pro)
SLC26A4	c.1693T > C (p.Cys565Arg)
ACADSB	c.443 C > T (p.Thr148Ile); het
CTC1	c.3019delC (p.Leu1007Cysfs*62)
GJB2	c.101T > C (p.Met34Thr)
GJB2 *CFTR*	c.101T > C (p.Met34Thr) c.1521_1523delCTT (p.Phe508del)
GJB2 *F11*	c.35delG (p.Gly12Valfs*2) c.901T > C (p.Phe301Leu) het
CFTR *SERPINA1*	c.3468G > A (p.Leu1156=) Pi*MS
GJB2	c.101T > C (p.Met34Thr)
GAA	c.1841 C
PAH	c.1241 A! G (p.7yr414Cys)
FAH	c.1021 C > T (p.Arg341Trp)
Continued	

Gene	Variant
SLC22A5	c.364G > T (p.Asp122Tyr)
HEXA *PAH*	c.739 C > T (p.Arg247Trp) c.136G > A (p.Gly46Ser)
EYS *SCL12A3 BCHE*	c.2528G > A (p.Gly843Glu) c.2573T > A (p.Leu858His) c.1072T > A (p.Leu358Ile)
F11	c.901T > C (p.Phe301Leu)
IVD	c.941 C > T
CNGB3	c.595delG (p.Glu199Serfs*3)
CPT2 *ACADM*	c.338 C > T (p.Ser113Leu) c.362 C > T (p.Thr121Ile)
PAH	c.320 A > G (p.His107Arg)
FAH	c.1021 C > T (p.Arg341Trp)
GAA	c.−32-13T > G
BBS1 *GBE1*	c.1169T > G (p.Met390Arg) c.1909 C > T (p.Arg637*)
PEX6	c.1802G > A (p.Arg601Gln)
GJB2 *FAN1*	c.101T > C (p.Met34Thr) c.2616del (p.Asp873Thrfs*17)
PMM2 CDG	c.422G > A (p.Arg141His)
SLC22A5	c.43G > T (p.Gly15Trp)
FAN1	c.1811 + 1G > T
BBS1 *SCL26A2*	c. 1169 T > G (p.Met390Arg) c.835 C > T (p.Arg279Trp)
DYSF *ARSA* *GAA*	c.4911 + 1G > T (p.?) c.465 + 1G > A (p.?) c.−32-13T > G (p.?)

Table 3. Recessive variants detected in 60 individuals. All variants were heterozygous.

pathway. It demonstrates that using genomics as an assessment tool to identify those at increased disease risk can be successfully integrated in this specific primary care setting.

Almost a quarter (22%) of participants had actionable gene variants that changed medical management and 41% had results that may have implications for drug prescribing.

Previous studies show that using exome and/or WGS detects an actionable genetic finding in 12–21% of individuals[17–19]. This variation in incidence may be explained by several factors such as study setting, participant selection, family history, number of genes analysed and variant annotation parameters. The only other study to date[8], assessing use of WGS in primary care was a randomised trial of 100 patients in the US. Healthy adults ($N = 100$) with no history of diabetes or cardiovascular disease were enrolled to either a family history (FH) only arm ($n = 50$) or FH and WGS ($n = 50$). WGS encompassed over 4,000 disease associated genes as well as carrier and pharmacogenetic variants. Among those who received genetic testing, 22% (11/50) were found to have a gene associated with a monogenic disease risk. Like our findings there was a high proportion, 48/50 (96%) of individuals with a pharmacogenomic variant yielding a nontypical response to at least one medication. The variants detected were rare and no alterations in cancer predisposition genes were found. Limitations of both studies include a limited sample size, a lack in diversity of both ethnicity and socioeconomic status (SES).

As such this is a small, self-selected cohort that confers some selection bias. For example, the cohort was predominantly of European ancestry and participants came from higher SES (by virtue of being a private practice and location) and that > 80% of participants paid for genetic testing plus the medical assessments.

The enriched participant population may also have been influenced by physician-based interests and upfront knowledge of a family history of cancer. Over 80% (90/104) of individuals had either personal or family history of cancer which may explain the relatively high number of LP/P variants detected in cancer predisposition genes.

These constraints illustrate the need for further research examining the integration of WGS in a wider primary care setting to more accurately assess clinical utility and its potential to improve patient care. Long-term follow-up data are also needed to assess the impact of such an intervention on changes in medication or new diagnoses.

Several studies[20,21] have reported on population based genetic screening of a limited number of genetic variants in diseases with high morbidity (breast/ovarian/colon cancer and familial hypercholesterolaemia). These have shown that a high proportion of variants are detected, often without a family history (e.g. 50% in the case of Manchanda et al.[22] and that identification of these variants offers a health economic benefit.

Based on family history, 40% of participants with actionable variants in cancer predisposition genes would not have been eligible for genetic testing on UK national guidelines in this report. This study shows an increased diagnostic yield and ability to identify individuals who otherwise would not have been flagged for prevention or screening.

We found that 58% of our participants are carriers of a single copy of an alteration in at least one gene that can cause a recessive condition when two faulty copies of the gene are present. Of these, 25% had a gene where carrier frequency is less than 1 in 70. This means they would not have been offered prenatal testing in

Gene	Number of variants detected	Drug(s)	Potential Action
CYP2C19 *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *13, *15, *16, *17, *18, *19, *22, *24, *25, *26, *28	*N* = 39 (37.5%) *N* = 30 (28.8%)	Clopidogrel Omeprazole Pantoprazole Tricyclic antidepressants Voriconazole Clobazam	Consider alternative anti-platelet agent Alter dose or choose alternative agent depending on metaboliser status
CYP2C9 *1, *2, *3, *4, *5, *6, *8, *9, *11, *12, *13, *15, *25, *31	*N* = 39 (37.5%)	Warfarin Phenytoin Diclofenac	Alter dose; close monitoring
CYP4F2 rs2108622	*N* = 52 (50%)	Warfarin Acenocoumarol Phenprocoumon	Alter dose; close monitoring
CYP2D6 *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *19, *20, *21, *29, *35, *36, *38, *40, *41, *44, *62, *xN	*N* = 21 (20.2%)	Codeine Tramadol Tamoxifen Amitriptyline Venlafaxine Flecainide Metoprolol	Consider alternative analgesic agent; alter dose
CYP2B6 rs3745274, rs2279343, rs2279345, rs28399499	*N* = 52 (50%)	Efavirenz Nevirapine Methadone	-
CYP3A5 rs776746	*N* = 8 (7.7%)	Tacrolimus Sirolimus	-
SLCO1B1 rs11045879, rs4149056, rs4149015	Intermediate function *N* = 32 (30.8%)	Simvastatin Pravastatin Rosuvastatin	Consider reduced dose
DPYD c.1905 + 1G > A c.2846 A > T	*N* = 4 (3.8%)	Capecitabine, 5FU	Dose adjustment
VKORC1 rs9923231	*N* = 20 (19.2%)	Warfarin	-
TPMT	*N* = 1 (0.96%)	Mercaptopurine, Thioguanine, Azathioprine	-
NUDT15 rs116855232	*N* = 2 (1.9%)	Azathioprine Mercaptopurine	-
UGT1A1 *1,*28,*36,*37	*N* = 4 (3.8%)	Irinotecan Atazanavir	-

Table 4. Pharmacogenomic variants detected in 104 individuals. Genes not detected in this cohort: *G6PD*, *CACNA1S*, *CFTR*, *RYR*.

some public health systems, including the UK. WGS does not detect all recessive genetic alterations included on a carrier panel (for example it cannot reliably determine spinal muscular atrophy carrier status) so it may be preferable to offer carrier testing for couples seeking maximum information for family planning.

We found clinically actionable pharmacogenomic variants that may alter drug prescribing in 41% of participants. Common drugs requiring dose modifications included proton pump inhibitors, warfarin, statins, some chemotherapy agents, and antidepressants. *CYP2C19* variants, associated with poor or intermediate metabolism of clopidogrel, were detected in 37.5% of patients. Studies show that in those with loss of function variants in *CYP2C19* an alternative anti-platelet drug can reduce atherothrombotic events particularly in percutaneous intervention and stroke[23,24]. NICE guidance has recently recommended the use of *CYP2C19* genotyping to assess suitability of clopidogrel in patients who had ischaemic stroke or a transient ischaemic attack[25].

Importantly, four participants were found to carry a *DPYD* variant that is associated with life-threatening adverse reactions if treated with fluoropyrimidine based chemotherapy, widely used to treat colorectal, breast, and pancreatic cancers. Limited testing of four common variants (derived from European populations) in the *DPYD* gene was introduced in the NHS in 2020[26]. We did not analyse *HLA* genes, which should optimally be added to a pharmacogenomic analysis, as they play a significant role in the pathogenesis of immune mediated adverse drug reactions.

We analysed PRS for four cancers (prostate, breast, ovary and colon). As expected, individuals with a previous diagnosis of one of these cancers, were more likely to be in the top 80% of the risk distribution. The use of PRS to risk stratify populations is a new area of research and studies are starting to report that it can be used to target populations to find clinically significant disease[27]. Further research will be needed to validate the utility of PRS for risk stratified management. The GenoVa study[28] will evaluate the clinical utility of PRS of 6 common diseases in a primary care setting in the US and assess implementation compared to standard care. In the UK, a

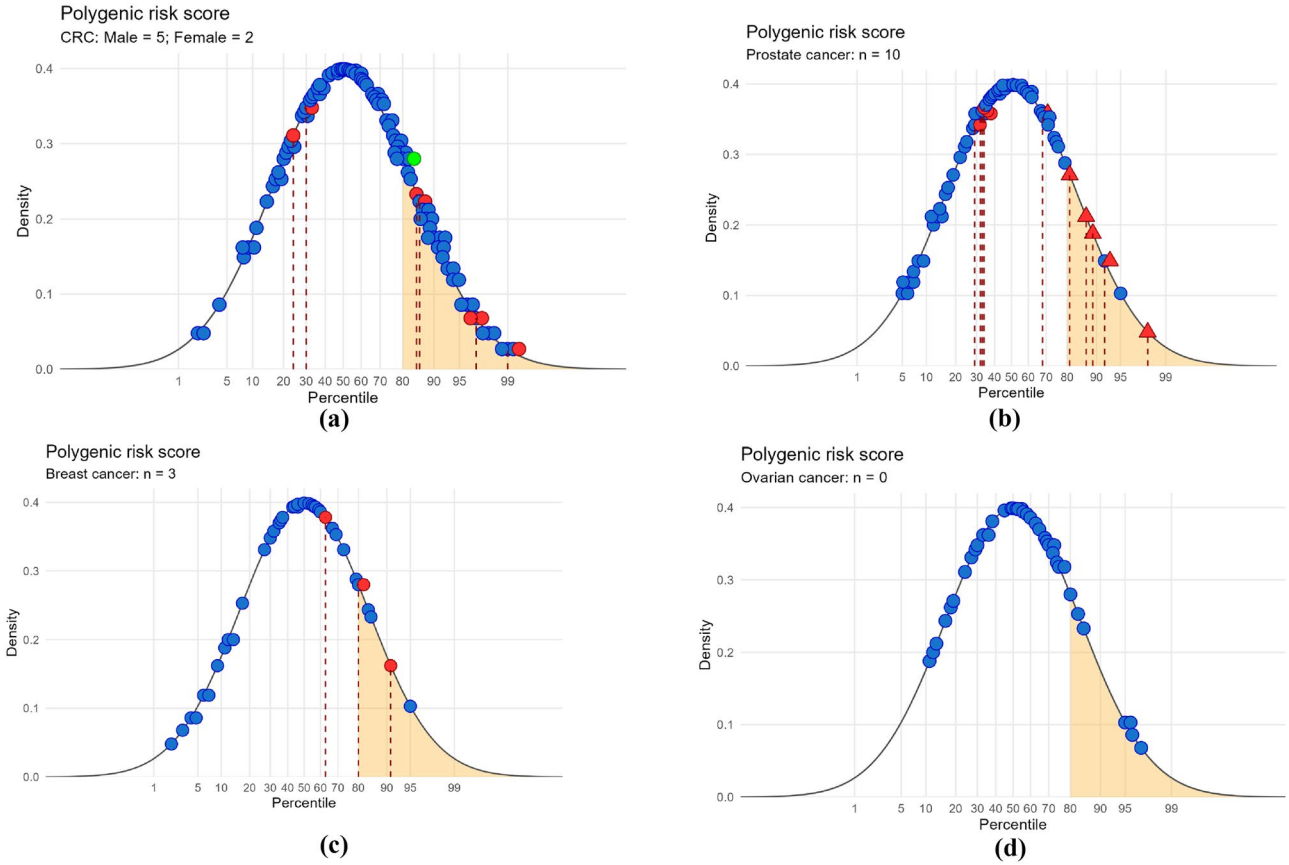

Fig. 1. **(a-d)** PRS The following are the bell curves showing the normal distribution of PRS expressed in percentiles, 1KG EU data served as reference population. Blue dots represent unaffected individuals. Orange shaded area shows the top quintile of PRS distribution. (**a**) Distribution of PRS for colorectal cancer (CRC) among male and female participants. Five male and two female individuals had cancer diagnosis before entering the study shown by red dots. One male individual had significant volume of polyps (shown in green). (**b**) Distribution of PRS for prostate cancer among male participants. Individuals with red dots had a prostate cancer diagnosis prior to study entry, individuals with red triangles had cancer diagnosis as a study participant as a result of recommended screening. The latter were seen in the prostate risk clinic at The Royal Marsden NHS Foundation Trust. (**c**) Distribution of PRS for breast cancer among female study participants. Individuals who had a diagnosis of breast cancer before entering the study are in red dots ($n = 3$). (**d**) Distribution of PRS for ovarian cancer among female study participants.

recent study using PRS for cardiovascular risk stratification has been shown acceptable by users and providers in primary care[29].

The findings of this study have important implications for expansion of genomic testing into the NHS as planned by Genomes England[1]. If WGS is to be integrated into primary care, there are several potential hurdles. This model pathway is labour intensive. As reported it is not affordable for widespread use in a public system. We have shown that integrating a virtual MDT with clinical genetic expertise from the NHS and private sector is realistic and integral for managing results.

Although a third of participants had a change of management after their medical assessment, the findings from the medical assessment and WGS were mutually exclusive.

From this limited series, the cardiac predisposition gene panel detected a low incidence of actionable variants in this population.

Our data suggest that an optimal refined test for use in a larger healthcare system could be a cancer and pharmacogenomics panel and a low pass whole genome for PRS calculations. Ideally, the WGS, when refined using long-read sequencing, may be able to detect those genetic variants which are due to copy number variation and large deletions/insertions and thus negate the use of concomitant panel genetic tests/whole exome analysis. As the efficacy of PRS becomes established[30] and its clinical utility determined, it will be important to continue to evaluate these in risk-based research screening initiatives.

This case series has shown that there is a potential actionability of using WGS data in a primary care setting where integration of data associated with holistic healthcare is paramount (Fig. 2). Although our model pathway is time intensive, it is feasible, and the experience can be used as a platform to design and implement further studies consisting of NHS practices serving more diverse communities using WGS into primary care. Further

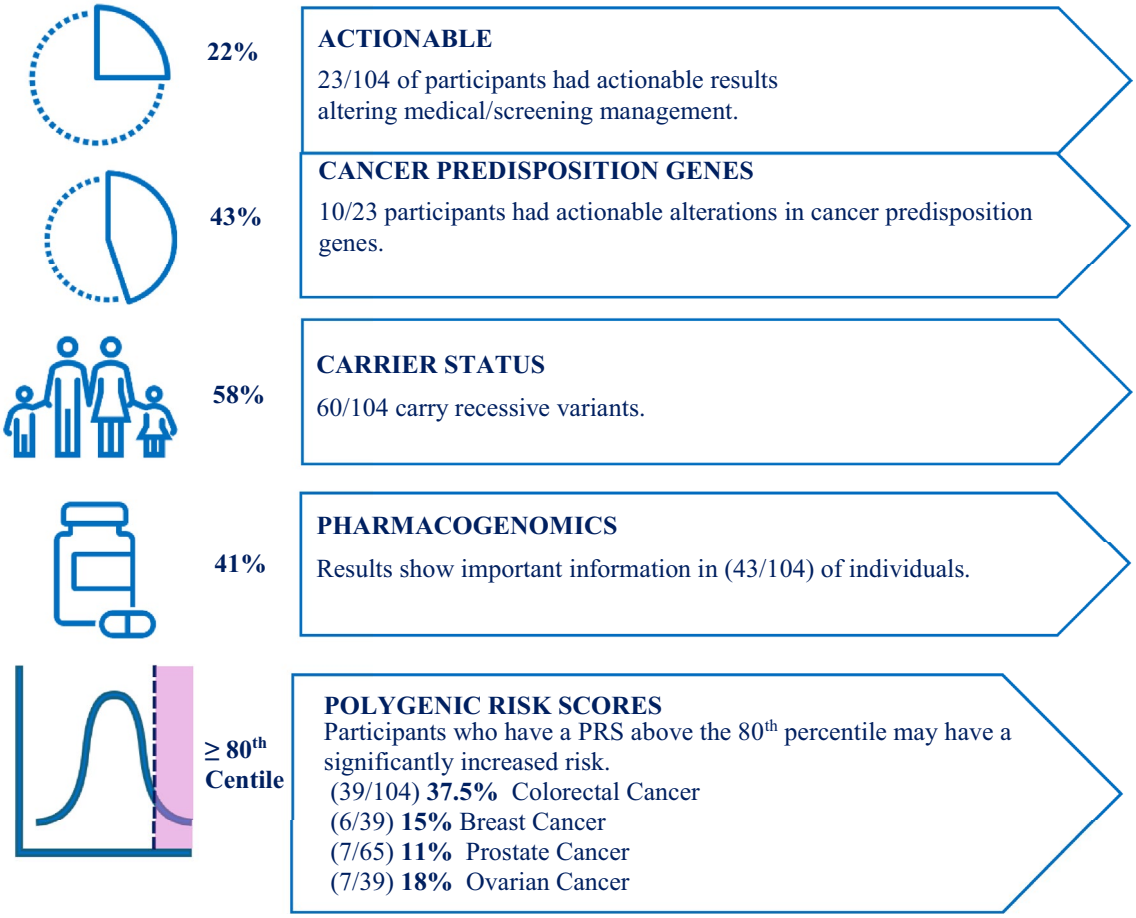

Fig. 2. Summary of WGS findings.

economic evaluation and longer-term outcomes are required to determine the cost-benefit ratio as a future test in public healthcare systems.

Methods

The 90 S study is a feasibility study that examines integrating WGS as an additional screening prototype in a private, general practice in London, United Kingdom (UK). The primary outcome is to determine the prevalence of clinically actionable coding germline variants found on WGS, based on the American College of Medical Genetics and Genomics (ACMG) guidelines[31] with modifications (i.e. variants in conditions that would change management).

Actionability was defined as a change in management of the patient's diagnostic, screening or treatment journey that could be instigated at the primary care level (for example, tertiary referrals, further cascade testing or adjustment in medication).

Individuals registered with the practice were approached by their GP for consideration of WGS. The setting is a private general practice providing individuals with a broad range of medical care. This practice was chosen as it has integrated echocardiography and visiting cardiologist review which could provide immediate interpretation of potentially life-threatening cardiac genomic findings. The practice also integrated abdominal ultrasound. Study entry criteria specified currently asymptomatic individuals, aged ≥ 25 years; those with active depression were excluded. Eligible individuals were provided with a participant information sheet explaining the study purposes and informed consent for all participants was obtained. The study was approved by the London Chelsea Research Ethics Committee (LREC 19/LO/0949) and conducted in accordance with relevant guidelines.

A focus group of the first 20 study participants (funded by research), using pseudonyms, was conducted virtually to assess user experience. Thereafter WGS was adopted as standard of care in the practice paid by the participants. WGS and medical outcome data were then assessed as a clinical evaluation with a revised research approval for the polygenic risk score (PRS) component (the analysis for this component remained research funded) of the programme. Those with an increased risk of prostate cancer/prostate cancer detected were managed in The Royal Marsden NHS Foundation Trust Prostate Risk Clinic. The subsequent 86 participants paid for their own WGS and imaging investigations as a standard of care service, and this was assessed as a model pathway.

Participants were counselled about underlying genetic contributions to the development of diseases related to the list of actionable genes as well as implications unique to both screening and genetic results for themselves and potentially their family members.

All participants underwent a medical assessment that covered past medical history, three generation family history, medication history, general systemic inquiry, and physical examination and routine blood tests. Men over the age of 50 had prostate specific antigen (PSA) testing. All patients had an ECG, echocardiogram, abdominal and pelvic ultrasound.

A virtual Multidisciplinary Team (MDT), consisting of four Clinical Geneticists, the General Practitioner, and Clinical Fellow reviewed all reports from WGS and clinical gene panels. An integrated MDT report was created as a summary to communicate genetic findings and action points for participants and their doctors. The flow chart of the participant pathway and MDT proforma are shown in Supplementary Fig. 1.

Testing process

Whole genomes were sequenced to at least 30X mean depth of coverage, with a minimum breadth of coverage of 95% of bases sequenced to at least 10X read depth, on a HiSeq X Ten System next generation sequencer, Illumina. The company's filtering method in the technical note, states: 'Initial filtering of variants is based on criteria, including population frequency, variant type, and variant classifications databases such as ClinVar and Human Gene Mutation Database (HGMD).The analytical pipelines categorise variants into discrete report sections that reflect overall impact of a variant on health. This is based on multiple factors including clinical significance, clinical actionability as defined by professional organizations and overall likelihood of developing disease' (www.veritasintercontinental.com). Only constitutional (germline) variants were reported. All analyses were performed by Clinical Laboratory Improvement Amendments (CLIA) or equivalent approved laboratories.

The sequencing company examined the WGS output for variants in genes from a list of consensus-derived, clinically valid 566 actionable genes (Supplementary Table 3). The list of actionable genes encompassed inherited cancers, cardiovascular diseases, haematological conditions, and genes associated with recessive conditions in clinical use, across the UK. It included the 59 ACMG recommended actionable genes relevant at that time and a subset of pharmacogenes that encompass 'actionable drug prescribing' (FDA approved drugs with published Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines[15]). Only likely pathogenic/pathogenic variants are reported from the WGS data, with interpretation based on current ACMG variant classification guidance[31]. *HLA* associated drug interactions were not analysed as it was not part of the Veritas Intercontinental pipeline.

WGS data enabled us to calculate PRS for four cancers that were conducted as a research activity and results fed back as research findings only (under separate research consent), as a relative risk (See supplementary material for methodology).

Clinical gene panel sequencing tests for cancer and cardiac associated conditions were also undertaken (details at www.invitae.com). This served as a clinical practice safeguard as WGS by short-read sequencing may miss large deletions (greater than 60 kb) and copy number variations. It also allows verification to enable immediate clinical action in high-risk LP/P variants. Panel tests reported variants of uncertain significance (VUS).

We did not interrogate genes associated with dementia or adult-onset neurological conditions such as Parkinson's disease as the difference prior knowledge of such conditions can make to change outcome is currently uncertain, compared with the burden of worry. The screen is not intended for use for reproductive decision making but does include 200 recessive disorders.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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Author contributions

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Declarations

Competing interests

COI Dr Sandberg is the Medical Director of 90 Sloane St and The London Genetics Centre at 90 Sloane Street which is a private general practice. The staff at 90 Sloane Street/London Genetics Centre are partly renumerated (a consultation fee) by individuals who had the whole genome screening as standard of care. Prof Eeles, Dr Jones, and Dr Bancroft were not renumerated by The London Genetics Centre for the work for this report. Prof Eeles has practising privileges for other private practice at 90 Sloane Street and The London Genetics Centre which is renumerated; this is a separate clinical pathway, and her affiliation above excludes The London Genetics Centre for this paper as this was an academic initiative and she did not receive renumeration from 90 Sloane Street or patients thereof for this work.Professor Rosalind Eeles has the following conflicts of interest to declare: Honoraria from GU-ASCO, Janssen, University of Chicago, Dana Farber Cancer Institute USA as a speaker. Educational honorarium from Bayer and Ipsen, member of external expert committee to Astra Zeneca UK and Member of Active Surveillance Movember Committee. She is a member of the SAB of Our Future Health. She undertakes private practice as a sole trader at The Royal Marsden NHS Foundation Trust, 90 Sloane Street SW1 × 9PQ (see above) and 280 Kings Road SW3 4NX, London, UK. Dr Gabriella Pichert was remunerated for discussing WGS results with patients but was not remunerated for her other work on the programme. Dr Lucy Side was remunerated for discussing WGS results with patients but was not remunerated for her other work on the programme. Dr Terri McVeigh was remunerated for a series of educational lectures provided to GPs at 90 Sloane Street. She did not receive direct payment for clinical activity, but remuneration for her consultations with patients was provided to her host institution. She was not remunerated for her other work on the programme.Miriam Leon was remunerated as a Veritas Intercontinental employee but was not remunerated for her other work on the programme.Dr. Luis Izquierdo was remunerated as a Veritas Intercontinental employee but was not remunerated for his other work on the programme.Bibiana Palao was remunerated as a Veritas Intercontinental employee but was not remunerated for her other work on the programme.Dr. Elena Góngora was remunerated as a Veritas Intercontinental employee but was not remunerated for her other work on the programme.Elena Ordoñez was remunerated as a Veritas Intercontinental employee but was not remunerated for her other work on the programme.Vincenzo Cirigliano was remunerated as a Veritas Intercontinental employee but was not remunerated for his other work on the programme.All other contributing authors have no conflicts of interest to declare.
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Additional information

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