

**Current detection rates and time-to-detection of all identifiable *BRCA*-carriers in the Greater London population**

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**Running Title**

Current detection rate and time to detection of all BRCA carriers

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## **ABSTRACT**

### **Background**

*BRCA*-carrier identification offers opportunities for early-diagnoses, targeted treatment and cancer prevention. We evaluate *BRCA*-carrier detection rates in General and Ashkenazi-Jewish(AJ) populations across Greater-London and estimate time-to-detection of all identifiable *BRCA*-carriers.

### **Methods**

*BRCA*-carrier data from 1993-2014 were obtained from NHS genetic-laboratories and compared with modelled predictions of *BRCA*-prevalence from published literature and geographical data from UK Office-for-National-Statistics. Proportion of *BRCA*-carriers identified was estimated. Prediction-models were developed to fit *BRCA*-detection rate data. *BRCA*-carrier identification rates were evaluated for an “Angelina-Jolie effect”. Maps for four Greater-London regions were constructed and their relative *BRCA*-detection rates compared. Models developed were used to predict future time-to-identify all detectable *BRCA*-carriers in AJ-&-general populations.

### **Results**

Till 2014, only 2.6%(3072/111742 estimated) general-population and 10.9%(548/4985 estimated) AJ-population *BRCA*-carriers have been identified in 16,696,608(AJ=190,997) Greater-London population. 57% general-population and 54% AJ mutations were identified through cascade-testing. Current detection rates mirror linear-fit rather than parabolic-model and will not identify all *BRCA*-carriers. Addition of unselected ovarian/triple-negative breast cancer testing would take >250 years to identify all *BRCA*-carriers. Doubling current detection rates can identify all ‘detectable’ *BRCA*-carriers in the general-population by year 2181, while parabolic and triple-linear rates can identify ‘detectable’ *BRCA*-carriers by 2084 and 2093 respectively. The linear-fit model can identify ‘detectable’ AJ carriers by 2044. We did not find an Angelina-Jolie effect on *BRCA*-carrier detection

rates. There was a significant difference in *BRCA*-detection rates between geographical regions over time ( $p < 0.001$ ).

### **Conclusions**

The majority of *BRCA*-carriers have not been identified, missing key opportunities for prevention/earlier diagnosis. Enhanced and new strategies/approaches are needed.

## Introduction

Mutations in *BRCA1/BRCA2* genes are associated with a high-risk of breast (BC) and ovarian cancer (OC) in women, as well as elevated risk of prostate and male-BC in men.[1, 2, 3] Identifying carriers is important because it offers the opportunity of early diagnosis and/or prevention to reduce the burden of *BRCA*-associated cancers in the population. Additionally, *BRCA*-carriers who develop cancer can be offered new targeted treatments such as PARP-inhibitors. For known mutation carriers there are a number of risk management options like preventive surgery for BC/OC,[4, 5] screening for BC,[6] chemoprevention with selective estrogen-receptor modulators,[7] lifestyle and reproductive advice incorporating breast feeding, contraception and opportunity to inform reproductive decision-making, including preimplantation genetic-diagnosis.[8, 9] The importance of prevention is magnified by the increasing costs of new drugs/treatment and persistent poor OC-survival rates. Additionally the number of OC and BC cases are expected to rise by 27% and 24% respectively in the UK; and 55% and 55% respectively globally by 2035, leading to an increase in overall burden of disease.[10]

Over the years health services have provided *BRCA1/BRCA2* -testing using predominantly family-history (FH) based clinical-criteria, with testing offered through specialised genetic services at *BRCA1/BRCA2* mutation probability thresholds of initially 20% and subsequently this was reduced to a probability threshold of 10%.[11, 12] Several risk-models/clinical-criteria[13, 14, 15] are widely used to calculate these probabilities to identify individuals eligible for testing. This strategy is dependent on people and their doctors being aware of their FH and acting on it, accuracy of FH, communication within/between families and timely referrals to clinical genetics.

To date the performance of a health-service in detecting *BRCA1/BRCA2* mutations compared to the estimated prevalence for an entire population in a large geographical area has not been assessed. We report on the *BRCA1/BRCA2* detection-rates across the entire Greater-London and bordering areas population since National-Health-Service (NHS) testing began from 1995-to-2014. We evaluate

the carrier identification rate across four geographical areas covered by NHS London regional genetic-services (RGS). We also for the first time forecast the time to pick up all identifiable *BRCA1/BRCA2*-carriers in the Greater-London and bordering areas population using current clinical protocols. These analyses are undertaken separately for both AJ and non-AJ general-populations.

## **Methods**

Data on *BRCA1/BRCA2*-carriers identified by genetic-testing through the NHS London genetics laboratories between August-1993 and November-2014 were obtained from laboratory records and databases. This included date of test, carrier postcode, AJ-ethnicity (self-reported) and mutated gene (*BRCA1/BRCA2*).

The first stage was to map the number of carriers identified in London by NHS providers over this period. In London, four NHS RGS and an independent NHS cancer-genetics centre provide clinical-genetics care to a Greater-London and bordering areas population. Each of the four RGS covers a distinct area (A,B,C,D) comprising of a set of different postcode-sectors.[16] People are referred to the relevant RGS depending on their postal-address that falls in one of the postcode-sectors. The independent NHS genetics-centre received referrals from all four areas (A,B,C,D). We constructed the map of these four coverage areas (A,B,C,D) based on postcode-sectors, using ArcGIS 10.4 software (Figure –1). Postcode-data of identified carries was matched to all known Greater-London and bordering areas postcodes in areas A,B,C,D. *BRCA*-carriers identified by the genetic laboratories from outside these four catchment-areas, were excluded from the analysis.

These detection-rate data were compared to modelled estimates of the number of carriers in each area. Incorporating information from improved/contemporary sequencing technologies, updated mutation pathogenicity and modifications in penetrance, we recently estimated that *BRCA1+BRCA2* prevalence in the general-population to be 0.00677(CI:0.0059-0.0077).[17] These estimates are in

line with data from cancer-free women controls from the Australian Lifepool study.[18] Ashkenazi-Jewish (AJ)-population data were obtained from our GCaPPS study which found *BRCA*-prevalence to be 0.0261(0.0173-0.0378).[19] A number of *BRCA*-carriers are missed by current clinical-criteria which are based on risk levels determined by FH. Recent estimates suggest only approximately 50% of general and 44% of AJ *BRCA1/BRCA2*-carriers[19] are 'detectable' using current clinical-genetics criteria. Population density data by boroughs and postcodes in the mapped Greater-London areas were obtained from the Office-for-National-Statistics (ONS) database. Data were obtained separately for both AJ and non-AJ general-populations. The Greater-London population served by the NHS RGS was estimated to be 16,696,608, of whom 190,997 are self-reported AJ (2011, ONS census).[20] Thus the detectable number of *BRCA1/BRCA2* carriers in the general-population is= $16505611 * 0.00677 * 0.5$  [CI: $16505611 * (0.0059) * 0.5$ ;  $16505611 * (0.0077) * 0.5$ ]. The identifiable number of *BRCA1/BRCA2* carriers in the AJ-population is= $190997 * 0.0261 * 0.44$  [CI: $190997 * (0.0173) * 0.44$ ;  $190997 * (0.0378) * 0.44$ ].

To forecast the length of time from 2015 onwards it would take to detect all carriers using current clinical-criteria we first plotted detection curves of the number of carriers detected by time (Figure-2). We then developed two different prediction models (Parabolic and Linear) in the general-&AJ populations to fit the *BRCA*-carrier detection-rate data in the four geographical catchment-areas (A,B,C,D). The first parabolic-model (equations below) fits the entire data set and reflects the dynamics of all carriers detected per year since testing began. However, detection rates appear constant for the last 6-8 years. The second linear-model (equations below) is fitted only for part of the data where the detection-slope became close to constant, i.e. from year 2008 onwards for the general population and 2006 onwards for the AJ-population (Figures:2a,2b). The models were then used to predict time taken to identify all 'detectable' *BRCA*-carriers in the general-&AJ populations from the year 2015 onwards. The modelling takes into account the change in population over time. We assume the population would change at the rate of change seen between 2001-2011 UK

census.[20, 21] Census data indicate the general-population would increase by 93,334/year and the AJ-population would decrease by 394/year across geographical areas A,B,C,D.

For the general-population, parabolic-fit for total *BRCA*-carriers detected is  $y = 277.67 - 124.76 * x + 10.98 * x^2$  (where  $x=1$ -year step from Jan-1993). While for the linear-fit,  $y = 668.3 + 313.7 * x$  (where  $x=1$ -year step from Jan-2008) curve provided best-fit for the data. For the AJ-population, the parabolic-fit was  $y = 7.271 - 10.12 * x + 2.128 * x^2$ , where  $x=1$ -year step from Jan-1996, while for the linear-fit,  $y = 91.67 + 52.07 * x$  approximated the data best, where  $x=1$ -year step from Jan-2006. Figures-2a,2b show linear/parabolic function curves fitting the data. In addition to the linear-fit which reflects current detection-rate, the time taken with doubled and tripled detection-rates compared to the current linear-rate were also explored for general-&-AJ populations. Precise date-of-detection was missing for 163(5.5%) general-population carriers and these were excluded from model development.

The relative detection-rates observed for people living across the four geographical-areas A,B,C,D (adjusted for total-population in each area) were compared over time. Mann-Whitney test was performed for the carriers detected in quarter-year windows, adjusted for the total-population in each of the four geographical-areas A,B,C,D. A sensitivity-analysis was also undertaken assuming missing RGS-status data from each genetic laboratory is distributed amongst the four areas in the same proportion as available data (Supplementary Table-S1).

Angelina Jolie's publicised decision to undergo a risk-reducing mastectomy created a media storm and public frenzy around *BRCA*-testing. We evaluated our data for an "Angelina Jolie" effect: change in detection-rate after she underwent risk-reducing mastectomy on 16.02.2013.

## **Results**

Between 1993 and 2014 NHS genetic laboratories identified 3297 *BRCA1/BRCA2* carriers in the general-population and 575 in the AJ-population. 27 AJ and 225 general-population *BRCA*-carriers

lived outside the RGS catchment areas and were excluded. Date of detection was available for 2916 of 3072 general and 548 AJ carriers residing in Greater-London/bordering areas. Of these 57%(1589/2798) general and 54%(266/491) AJ mutations were identified through cascade-testing (testing a known mutation in the family). Three general-population and six AJ-carriers had mutations in both *BRCA1*-&-*BRCA2* genes. Overall 51%/62% *BRCA1* and 49%/37% *BRCA2* carriers belonged to general/AJ populations respectively. The *BRCA*-carrier detection curves over time for general-&-AJ populations are given in Figure-2a, Figure-2b respectively. The estimated 'total' prevalence of *BRCA*-carriers in Greater-London (areas:A,B,C,D) is 111742(CI:97383,127093) in the general-population and 4985(CI:3304,7220) in the AJ-population. Of these the 'detectable' number using clinical-criteria is estimated as 55872(CI:48692,63547) in the general and 2193(CI:1454,3177) in the AJ-population respectively. The residual 55870 general and 2792 AJ carriers remain undetectable.

Figure-1 shows a map of the Greater-London and bordering postcodes lying within the four geographical areas A,B,C,D. Table-1 provides the overall population and estimated carrier distribution across these four areas. Figure-3 and Figure-4 depict the forecasting models of the time-to-detect the remaining *BRCA*-carriers from 2015 onwards for the general and AJ-populations respectively across the greater London-&-bordering areas. Each figure shows outcomes of linear and parabolic models and also where the linear-rate is doubled or tripled. Line-'a' reflects the total estimated carriers in the population and Line-'c' reflects the 'detectable' carriers. 'Line-a'-'Line-c' denotes the unidentifiable pool of *BRCA*-carriers using FH-based clinical-criteria. The current NHS detection-rate mirrors the linear function as the slope is near constant over the last 8years (Figures:2a,2b). Continuing at the current 2014 NHS detection-rate, will not be able to identify the 'detectable' *BRCA*-carriers in the non-AJ general-population. Doubling these rates will enable identification of 'detectable' *BRCA*-carriers by the year 2181 (CI:2141,2228), while the parabolic and triple-linear rates can identify the 'detectable' *BRCA*-carriers in the population by 2084 (CI:2077,2091) for parabolic or 2093 (CI:2077,2112) for tripled-linear rate. The current detection-

rate for AJ-carriers will identify 'detectable' carriers by 2044 (CI:2032,2060), while doubling this linear-rate can do so by 2025 (CI:2019,2034).

The detection-rates of *BRCA*-carriers over time across the four-areas A,B,C,D are plotted in Supplementary-Figures-S1a,S1b for general-&AJ populations respectively. Corresponding RGS-area status information was missing for 22(4%) AJ and 675(23%) general-population *BRCA*-carriers. Hence, the analysis comparing rates across different areas A,B,C,D is limited to 96% AJ and 77% general-population carriers. Comparisons of the mean-performance in quarter-year windows (as a ratio from all detectable carriers) are presented in Table-2. There was a significant difference in *BRCA*-carrier identification rates amongst people living across the four-areas A,B,C,D over time.

Although we saw a numerical increase in the average quarter-year *BRCA* detection-rates in the 18months after compared to 18months before "Angelina Jolie's" mastectomy, this was not statistically significant for either the general (100 vs 85.7,p=0.059) or AJ populations (13 vs 12.8,p=0.612).

## **Discussion**

We for the first time report on NHS *BRCA*-carrier identification-rates across the Greater-London/bordering population over time. Over the years, only 2.6% of total estimated-carriers and 5.1% of detectable-carriers have been identified in the general-population. Greater success has been achieved in the AJ-population with 10.9% of total-estimated and 24.9% of detectable AJ-carriers being identified. Nevertheless, the significantly large majority of *BRCA*-carriers at high-risk of cancer remain to be identified. Although the parabolic-model has a steeper curve and quicker detection than the linear-model, the current detection-rates mirror a linear-slope far more rather than a parabolic one. Continuing at the 2014 identification-rate, the NHS is unable to identify the 'detectable' pool of *BRCA*-carriers in the general-population, while it will take 30years to identify the 'detectable' *BRCA*-carriers in the AJ-population. However, we expect the current detection rates to increase given the lowering of the *BRCA1/BRCA2* probability threshold for genetic-testing to 10% in 2013 and the recent introduction of mainstreaming of *BRCA1/BRCA2* testing for OC-cases. The full

impact of this will emerge over the next few years and is therefore probably underestimated in our base case analysis. Nevertheless, even if the rate doubled it will take ~167 years to identify the detectable pool of *BRCA*-carriers and if it tripled it could still take 79years, with an exponential parabolic increase making it 70years to identify 'detectable' *BRCA*-carriers in the general-population. To expect a tripling or exponential increase is unrealistic. Most of the carriers who do not fulfil FH-based clinical-testing criteria will however remain undetected. Various reasons for historic lower detection-rates include poor performance characteristics of clinical-criteria (limited sensitivity), less sensitive molecular tests, paternal inheritance, small family-size, incomplete penetrance, poor communication within/between families, population migration, poor physician/health-professional awareness, poor referral guideline implementation by non-genetic/primary-care clinicians, limited public awareness and population preferences.[19, 22] The rate-of-detection currently being achieved is not adequate to maximise *BRCA*-carrier identification for cancer screening and prevention.

Around 10% epithelial-OC[23] (84% of OC)[24] and 9.8% triple-negative(TN) BC[25] (13.5% of BC)[25] unselected for FH have *BRCA*-mutations. Testing is now advocated in them from 2015 in the UK.[26] This approach will also enable identification of *BRCA*-carriers lacking a strong FH. Our study population comprises 26.4% of the UK population.[20] Assuming proportionate UK annual OC-&-BC incidence in our population (OC-incidence=0.264\*7400; TNBC-incidence=0.264\*55200)[27, 28] and two additional carriers identified from cascade testing[29] for each index-case, we incorporated the additional impact of testing all epithelial-OC and TNBC in the models to detect 'total' *BRCA*-carriers in the population. Addition of testing epithelial-OC/TNBC at cancer diagnosis to current detection-rates, will take >250years (2286) to identify the 'total' *BRCA*-carriers in the general-population. Coupled with the doubled-linear fit, tripled-linear fit and parabolic-fit, 'total' *BRCA*-carriers could be detected by 2226, 2181, and 2128 respectively. Hence, even if 'everyone' is tested at cancer diagnosis, it will take an inordinately long time to identify all at-risk *BRCA*-carriers.

Our study has a number of advantages. We incorporate data since NHS *BRCA*-testing began. We use most recent estimates of *BRCA1/BRCA2* mutation frequencies for the AJ[19] and general-populations,[17] and incorporate the potential change in population size over time. Limitations include exclusion of any *BRCA*-testing in the private sector. Unfortunately these data are unavailable/inaccessible. However, most *BRCA*-testing in the UK health-system is undertaken through the NHS. The private health-sector is miniscule compared to the public NHS. According to the King's fund only ~11% of UK-residents have some private medical insurance. However, that does not equate to 11% of *BRCA*-testing being done privately and the proportion of private *BRCA*-testing is probably much lower. A sensitivity-analysis assuming 11% additional *BRCA*-carriers identified through other sources indicates that doubling or tripling the linear-model would detect general-population carriers by 2146(CI:2116,2185), or 2080(CI:2067-2095) respectively. Additionally all identifiable AJ *BRCA*-carriers could be detected by 2040(CI:2029-2055). This does not majorly shift the time-to-detection estimates predicted using our models. We cannot account for predictive-testing undertaken by family members living outside London. However, the analysis incorporates cascade-testing of London-based individuals whose familial mutation may have been diagnosed outside London. Unlike some reports we did not find an 'Angelina Jolie' effect translating to a higher carrier detection-rate.[30] Nevertheless, this is consistent with other findings of increased genetic-testing referrals from the worried well, with many not fulfilling testing criteria.[31]

Our analysis is not limited/restricted by age of testing. Our data set had anonymised data without date of birth or age distribution of carriers. This may be considered as a limitation by others. However, predictive pre-symptomatic testing for *BRCA* mutations is currently offered in the UK from the age of autonomous consent i.e. 18 years.[32, 33, 34] This is consistent with many international guidelines.[35, 36, 37, 38, 39] This is a time series analysis spanning up to 250 years in the prediction models. Within 18 years' time someone who is <1 year old will become eligible for testing. Limiting

testing to say  $\geq 30$  years in our view is a paternalistic approach. Potential clinical benefits for testing between the ages of 18 and 30 years include, the opportunity to make contraceptive, lifestyle and reproductive choices including PGD that can minimise risk. Earlier awareness can help decision making in some women who may choose to complete their families earlier so as to have timely surgical prevention later. Taking the pill at younger ages (rather than  $>30$ ), at a lower absolute risk of breast cancer will have a lower detrimental impact on breast cancer risk while providing the benefit of ovarian cancer risk reduction. Experience from clinical practice as well as our population testing research trials support and show acceptability of genetic testing from 18 years.[19, 40, 41] There is no upper age limit for *BRCA* testing in the UK. The annualised risk of developing ovarian cancer is  $\sim 1\%$  per annum in the older age group. The average life expectancy in women is  $\sim 85$  years, and statistically this is even greater in older women. Hence the residual risk is still high enough to offer surgical prevention and many older women  $>70-75$  years attending our clinics opt for this. 40% of ovarian cancers occur in the  $>70$  age group and 28% in the  $>75$  years age group.[42] *BRCA* carrier identification even in older women offers the opportunity for predictive/cascade testing for other unaffected family members with implications for screening/prevention and cancer risk-reduction. Additionally this has implications for their care with respect to improving survival through use of drugs like PARP inhibitors. Hence, for these reasons we feel the analysis should not be restricted by age.

Our data show regional differences in identification of *BRCA*-carriers across London. Identification-rates were higher amongst AJ and general-population people living in C-&-D postcode-sectors than those within areas A-&-B. A limitation of the analysis is incomplete RGS data for 23% general-population carriers. However, a sensitivity-analysis assuming proportionate attribution of RGS to these 23% carriers detected does not change the variation in carrier identification rates observed between different London regions (Supplementary-Table-S1, Figures-S2,S3). The precise reasons for why apparently more people living in areas C-&-D come forward for testing compared to areas A-&-

B cannot be evaluated through this analysis and require further study. We had access to limited anonymised data and lacked broader individual carrier-level variables/factors to properly analyse socio-economic or population factors affecting testing uptake across different areas. We also lacked information on total number of *BRCA*-tests undertaken (including those testing negative). There are socio-economic differences in populations across different London areas. The Index-of-Multiple-Deprivation (IMD) incorporates seven domains to produce an official measure for relative deprivation across small areas. The majority of the London areas present amongst the 20% most deprived in the country are represented across area-A postcodes, followed by area-B and then area-C. The least deprived being in area-D postcodes.[43] Differences in population characteristics, socio-economic status, knowledge, awareness, population attitudes itself may contribute to this disparity observed in testing and detection-rates. Additional contributory factors include NHS structural changes with genetic-clinics in some areas being established a few years after others and in part oncology services through which the affected proband carrying the familial mutation is ascertained. There is limited awareness of *BRCA* testing amongst clinicians/practitioners and the population per se. Low referral rates for genetic counselling and subsequent *BRCA* testing have been reported by others too, which further highlights the missed therapeutic and prevention opportunities.[44] Understanding reasons for differences observed is important and requires further research. This can help plan interventions to address underlying issues and improve carrier identification.

The number of OC/BC cases are predicted to rise by 27%/24% respectively in the UK; and 55%/55% respectively globally, over the next 20years.[10] *BRCA*-carriers have a 17-44% OC-risk and 69%-71% BC-risk by 80-years.[1, 2] Uptake of screening and prevention options is cost-effective in reducing BC-&-OC incidence.[45, 46] Hence, *BRCA*-carrier identification driven precision-medicine and cancer prevention provides an excellent opportunity to reduce future cancer burden and improve health outcomes, the importance of which is magnified by current economic/funding constraints (2.4% NHS budgetary shortfall).[47]

The limited Greater-London *BRCA* detection rates achieved and long predicted time-to-identification observed highlights a need for change. We postulate that a similar situation probably exists across many other parts of the UK, Europe and other Western countries. Concerted efforts are required to increase knowledge and awareness amongst health-professionals (hospital specialists and primary-care general practitioners) the general public regarding current access, guidelines and health-system pathways for *BRCA*-testing. Additional steps are needed to simplify access and expand availability of *BRCA*-testing, including, investment in genetics infrastructure/services, relaxing current clinical-testing thresholds, as well as implementing new ascertainment strategies like testing at cancer diagnosis.

Systematic population-based testing has been advocated as one key innovative strategy. Population-testing can identify the large pool of carriers who remain undetected using FH-based approaches. It would also provide a strong stimulus to push carrier detection-rates to higher levels compared to current trends, providing a greater impetus for earlier identification and consequent OC/BC prevention. Next-generation-sequencing technologies and advanced bioinformatics now enable population-testing. In the AJ-population this has been, and found to be acceptable, safe, effective and cost-saving.[19, 22, 48, 49, 50] While population-testing should be implemented in the AJ-population, further research is needed before implementation in the general non-AJ population. A pilot-study is underway in the UK.[41] We recently showed that such an approach of population based genetic testing would be cost-effective in the general non-Jewish population too.[51] We call for research studies to understand the overall impact, and evaluate delivery mechanisms and pathways for a population-based *BRCA*-testing strategy in the general-population.

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The study was in part funded by 'The Eve Appeal' charity [GTCV]. The funding body (The Eve Appeal charity) had no role in the study design, data collection, analysis, interpretation, writing of the report or decision to submit for publication. The research team was independent of funders.

### **Ethics Approval**

This analysis was approved under the ethics approval obtained for the Genetic Cancer Prediction through Population Screening (GCaPPS) study, from the Institute of Child Health/ Great Ormond Street Hospital Research Ethics Committee: REC Reference number 08/H0713/44.

### **Contribution to authorship**

RM developed concept and design of the study. RM, RT, CJ, FG, CG, OB, AZ, VSG, MB, IJ were involved in conduct of the study. RT, CJ contributed data to the study. FG, CG helped with data collection. OB, AZ and RM developed the models. RM, OB, FG, VSG, AZ, MB, contributed to data analysis and preparation of figures and tables. RM, OB prepared the initial draft of the manuscript. All authors contributed to reporting of the work, including paper writing and critical review of the analysis. All authors approved the final version of the manuscript. RM and OB are guarantors of the work.

### **Competing Interest Statement**

IJ and UM have a financial interest in Abcodia, Ltd., a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. IJ is a member of the board of Abcodia Ltd, a Director of Women's Health Specialists Ltd and received consultancy from Beckton Dickinson. RM declares research funding from The Eve Appeal and Cancer Research UK into population testing and from Barts & the London Charity outside this work, as well as an honorarium for grant review from Israel National Institute for Health Policy Research. The other authors declare no conflict of interest.

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## **Transparency declaration**

The corresponding author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## **Data sharing**

Relevant anonymised data can be obtained on reasonable request from the corresponding author.

**Table-1: Population and estimated BRCA carrier distribution by four London areas A, B, C, D**

<b>London Area</b>	<b>Total General Population</b>	<b>Total AJ Population</b>	<b>Total Estimated BRCA carriers General Population</b>	<b>Total estimated BRCA carriers AJ Population</b>	<b>Detectable BRCA carriers General Population</b>	<b>Detectable BRCA carriers AJ Population</b>
<b>A</b>	<b>4545545</b>	<b>60135</b>	<b>30773</b>	<b>1570</b>	<b>15387</b>	<b>691</b>
<b>B</b>	<b>4467689</b>	<b>110796</b>	<b>30246</b>	<b>2892</b>	<b>15123</b>	<b>1272</b>
<b>C</b>	<b>3825404</b>	<b>9170</b>	<b>25898</b>	<b>239</b>	<b>12949</b>	<b>105</b>
<b>D</b>	<b>3666973</b>	<b>10896</b>	<b>24825</b>	<b>284</b>	<b>12413</b>	<b>125</b>
<b>TOTAL</b>	<b>16505611</b>	<b>190997</b>	<b>111742</b>	<b>4985</b>	<b>55872</b>	<b>2193</b>

AJ- Ashkenazi Jewish

**Table-2: Comparison of BRCA identification rates across four London areas A, B, C, D**

<b>General Population</b>					
<b>London Area</b>		<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>
	<b>Means</b>	<b>0.00051</b>	<b>0.00083</b>	<b>0.00115</b>	<b>0.00183</b>
<b>A</b>	<b>0.00051</b>		<b>p&lt;0.001</b>	<b>p&lt;0.001</b>	<b>p&lt;0.001</b>
<b>B</b>	<b>0.00083</b>			<b>p=0.014</b>	<b>p&lt;0.001</b>
<b>C</b>	<b>0.00115</b>				<b>p&lt;0.001</b>
<b>D</b>	<b>0.00183</b>				
<b>Jewish Population</b>					
<b>London Area</b>		<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>
	<b>Means</b>	<b>0.0053</b>	<b>0.0038</b>	<b>0.0243</b>	<b>0.0122</b>
<b>A</b>	<b>0.0053</b>		<b>p=0.078</b>	<b>p&lt;0.001</b>	<b>P=0.003</b>
<b>B</b>	<b>0.0038</b>			<b>p&lt;0.001</b>	<b>p&lt;0.001</b>
<b>C</b>	<b>0.0243</b>				<b>p&lt;0.001</b>
<b>D</b>	<b>0.0122</b>				

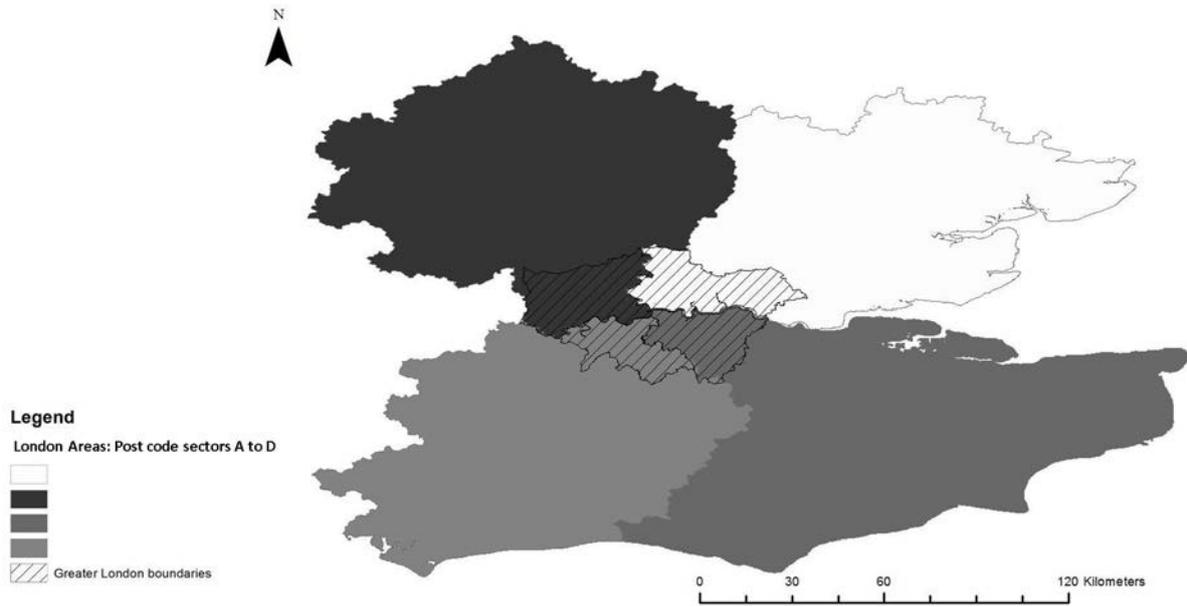
Table-2 compares mean slope of carriers detected in quarter-year windows, adjusted for the total *BRCA* carriers in the population living in the four different London areas. P values of Mann Whitney tests are given in the different cells. The top half of the table reflects data for the general population and the bottom half data for the Jewish population.

For the general population *BRCA* detection seen within people living in Area D > Area C > Area B > Area A.

For the AJ population *BRCA* detection seen within people living in Area C > Area D > Area B or A (Table-2).

**Figure 1: Map of London coverage areas (A, B, C, D)**

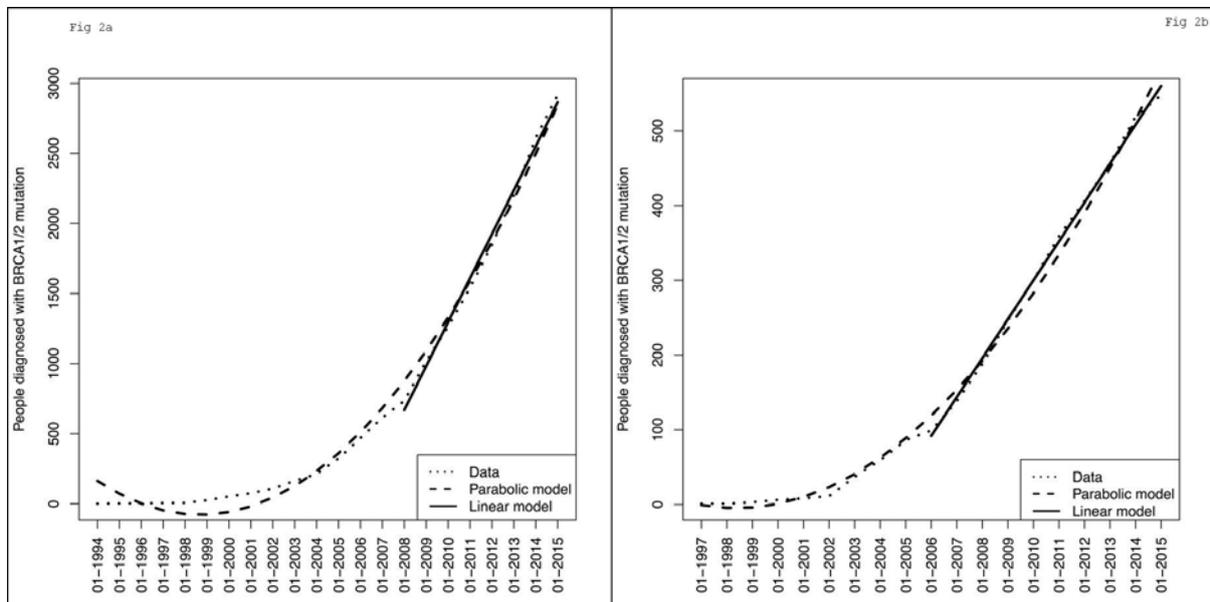
Greater London post code areas A, B, C, D covered in the analysis



**Figure 2: Number of carriers identified by time in the General and Ashkenazi Jewish populations in London and greater London**

Figure 2a: Number of carriers identified by time in the general population in London and greater London. The figure shows the fit of Linear and Parabolic curves to the *BRCA* carrier detection rate data in general population. X axis: Number of carriers detected. Y axis: Date of detection.

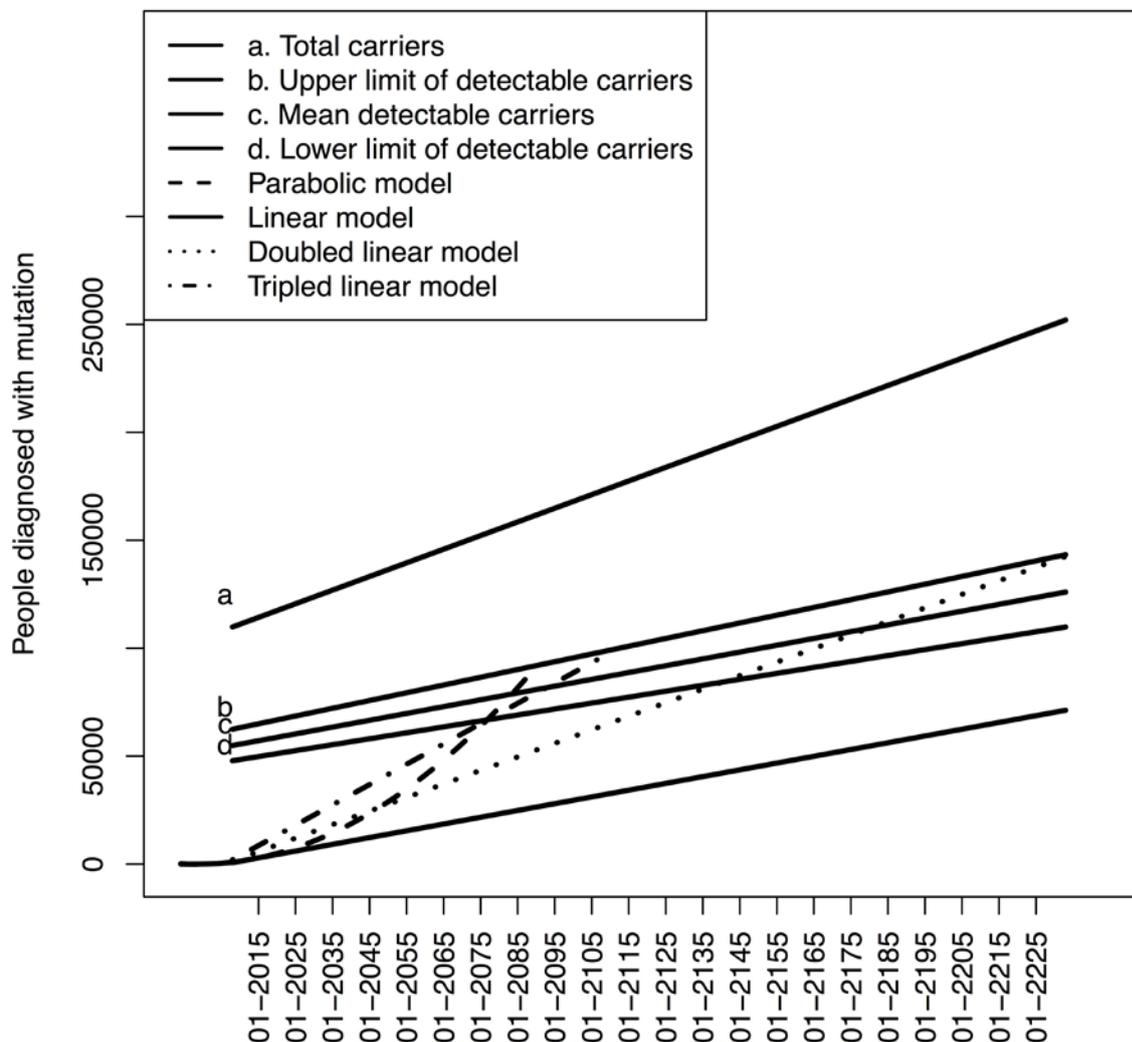
Figure 2b: Number of carriers identified by time in the Ashkenazi Jewish population in London and greater London. The figure shows the fit of Linear and Parabolic curves to the *BRCA* carrier detection rate data in the Ashkenazi Jewish population. X axis: Number of carriers detected. Y axis: Date of detection.



**Figure 3: Time to detection from 2015 onwards for the remaining estimated *BRCA* carriers in the general population across London and greater London.**

Figure-3 shows the predicted time to detection outcomes of parabolic, linear, double linear and triple linear prediction models for *BRCA* carriers in the general population. Line a- reflects the total estimated carriers in the population. Line c- reflects the detectable carriers. Lines b and d are the upper and lower confidence limits for Line c. Line 'a – c' reflects the unidentifiable pool of carriers using FH based clinical criteria.

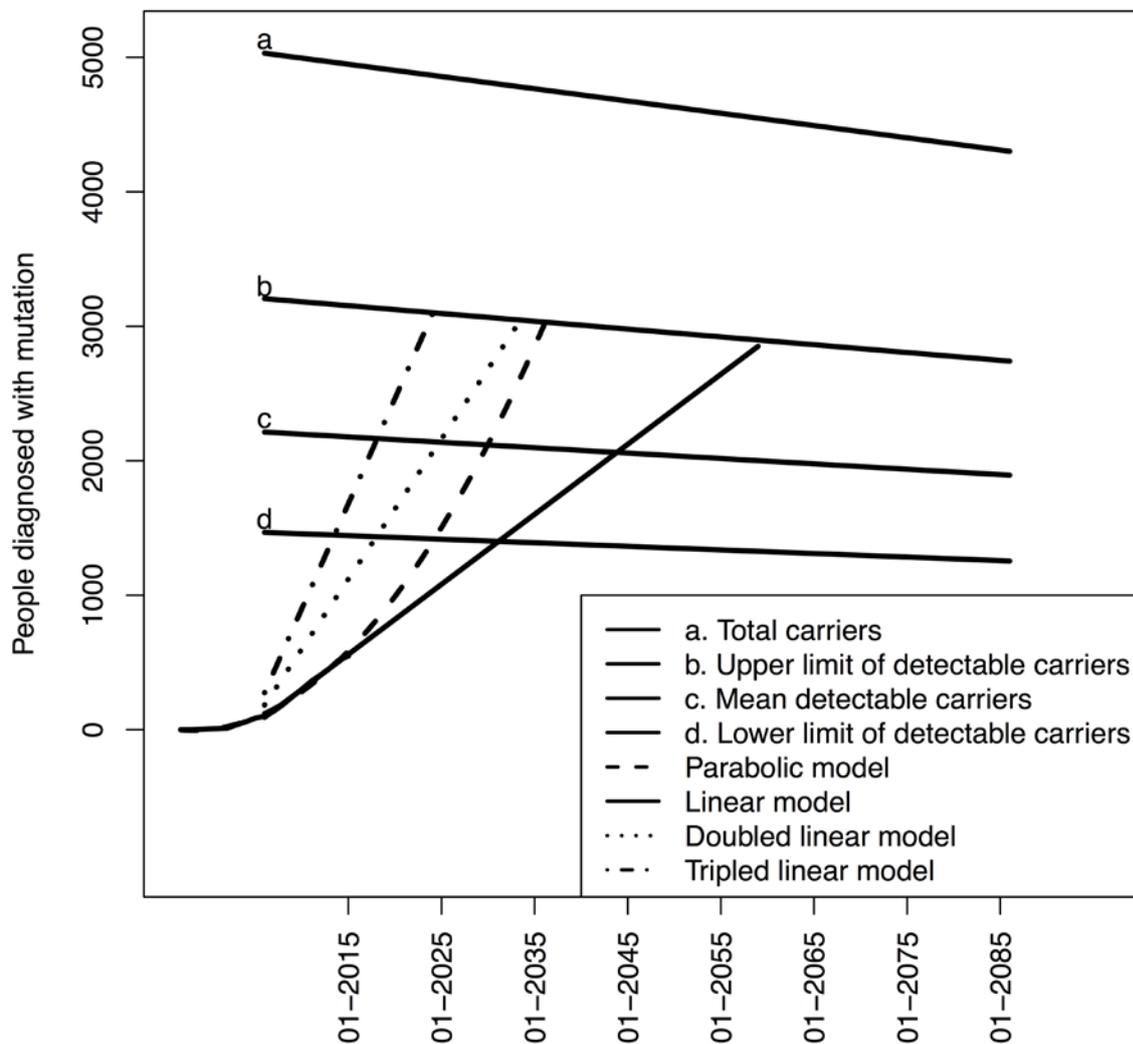
The detectable *BRCA* carriers in the general population cannot be identified by the linear model. A double linear rates will enable identification of 'detectable' *BRCA*-carriers by the year 2181 (CI:2141, 2228). The parabolic and triple linear rates will identify the 'detectable' *BRCA*-carriers in the population within 100 years. This will occur by the year will be 2084 (CI: 2077, 2091) with the parabolic or year 2093 (CI: 2077, 2112) with the tripled linear rate model.



**Figure 4: Time to detection from 2015 onwards for the remaining estimated *BRCA* carriers in the Ashkenazi Jewish population across London and greater London.**

Figure-4 shows the predicted time to detection outcomes of parabolic, linear, double linear and triple linear prediction models for *BRCA* carriers in the Ashkenazi Jewish (AJ) population. Line a- reflects the total estimated carriers in the AJ population. Line c- reflects the detectable carriers. Lines b and d are the upper and lower confidence limits for Line c. Line 'a – c' reflects the unidentifiable pool of carriers using family history based clinical criteria.

The linear fit model can identify detectable carriers by the year 2044 (CI: 2032-2060). The doubled linear rat model can do so by year 2025 (CI: 2019-2034), and tripling it could do so by year 2019 (CI: 2014-2025). The Parabolic model could potentially detect the detectable carriers by year 2030 (CI: 2025-2037).



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