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Feasibility and outcomes of the DNA Screen nationwide adult genomic screening pilot

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Population genomic screening enables the identification of individuals at high risk of medically actionable conditions before disease onset, yet real-world feasibility studies are lacking. Informed by prior cost-effectiveness modelling, we conducted a prospective nationwide pilot targeting young adults in Australia (aged 18–40 years), offering genomic screening for ten genes linked to hereditary breast and ovarian cancer, Lynch syndrome and familial hypercholesterolaemia. Of 30,017 registrants, 18,573 were invited and 10,263 completed genomic screening (median age 31.9 years, 45.5% men, 30.0% culturally or linguistically diverse). Here we detected pathogenic or likely pathogenic variants in 202 (2.0%). Of the 189 referred for clinical follow-up, 97.9% accepted and 87.3% attended appointments. Notably, 74.5% of attendees were ineligible for government-funded criteria-based genomic testing. Our findings demonstrate the feasibility of adult population genomic screening, including high public engagement, clinical uptake and identification of individuals ineligible for current criteria, supporting the further development of adult population genomic screening in Australia.

In Australia and other countries with national healthcare systems, publicly funded genetic testing in adults is typically limited to individuals who meet specific clinical criteria owing to a personal diagnosis and strong family history. While this targeted approach identifies pathogenic or likely pathogenic variants (PLPVs) in some individuals who meet these criteria, most individuals with PLPVs in the general population remain unidentified, even for commonly tested medically actionable conditions[1–5]. Cascade predictive testing, which involves testing for specific familial variants in the biological relatives of individuals with known PLPVs, can facilitate broader identification of individuals at high genetic risk, but is inherently constrained by the number of index cases detected[6]. Additional barriers including familial communication, testing cost, clinician awareness and complex referral processes further restrict testing access[7,8]. Private and direct-to-consumer testing options exist, but raise concerns about cost, equity, clinical validity and lack of follow-up care[9,10].

Population genomic screening, when aligned with established screening principles[11] and delivered with appropriate medical

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oversight, has been proposed as a new strategy to identify individuals at high genetic risk more broadly in the general population[12,13]. The US Centers for Disease Control and Prevention has designated hereditary breast and ovarian cancer (HBOC), Lynch syndrome (LS) and familial hypercholesterolaemia (FH) as 'tier 1' conditions, and proposed these as a starting point for population genomic screening in adults[12]. These conditions are linked to interventions that are proven to reduce morbidity and mortality[14–19] but are often molecularly underdiagnosed. Health-economic modelling suggests that offering combined genomic screening for HBOC, LS and FH may be cost-effective in different healthcare systems[20,21], especially those with national coverage[21–24]. However, real-world feasibility studies are lacking, especially in the setting of a national public healthcare system. So far, most population genomic screening studies have instead been conducted in US private healthcare settings, with many studies having retrospective designs and limited demographic diversity[2,3,25–32], or in Jewish populations[33,34].

Australia's national public healthcare system, population size (27 million) and existing screening frameworks[11] provide a suitable context for evaluating the feasibility of population genomic screening of young adults. Our prior modelling indicates that in Australia, offering population genomic screening for HBOC, LS and FH to younger adults, particularly those aged 18–40 years, would optimize early detection and prevention and yield the greatest benefit in terms of cost-effectiveness and long-term health outcomes[22]. The strategy of targeting young adults is also supported by modelling in the US system[20]. Accordingly, the DNA Screen national pilot was designed to assess the feasibility of offering genomic screening to a diverse population of young adults aged 18–40 years in Australia. The programme was designed in partnership with consumers, clinical geneticists and public health experts to maximize accessibility and remove testing barriers to the public. The aims of the study were to (1) pilot the implementation of population genomic screening in a national healthcare system to identify individuals with PLPVs aged 18–40 years, provide them with genetic counselling, refer them to partner clinical genetic services and evaluate the uptake of clinical appointments and follow-up care; and (2) determine the proportion of identified individuals with PLPV who, before enrolment in the study, would not have been eligible for any Australian government-funded genetic testing based on existing clinical criteria.

Results

Enrolment and demographics

Informed by prior cost-effectiveness modelling[20,22], we invited recruitment from young Australian adults aged 18–40 years between August 2022 and July 2024, from a nationwide estimated base population of 8,324,242 individuals. Following 1 day of national media coverage, 30,017 individuals registered to participate—15,899 in the first 48 h and an additional 4,550 in the first week. Promotion of the study was then discontinued, given the designated target (10,000 participants) had been exceeded. Registration was kept open as a 'waiting list', and another 9,568 individuals registered over the following 2 years with no active recruitment.

Registrants spanned all Australian states and territories, including remote areas. Of those who registered, 42.3% were from culturally or linguistically diverse (CALD) backgrounds. This was defined, using the Australian Bureau of Statistics census definition[35], as individuals either born outside of Australia, or speaking a language other than English at home, enabling direct comparison of the cohort's demographic characteristics with national census data. Of those who registered, 36.3% were born outside Australia and 27.9% spoke languages other than English at home (>80 languages). The main countries of birth outside Australia were China (18.3%), India (2.7%), the UK (1.7%) and Malaysia (1.5%). Demographic characteristics of the 30,017 individuals who registered to participate are summarized in Extended Data Fig. 1.

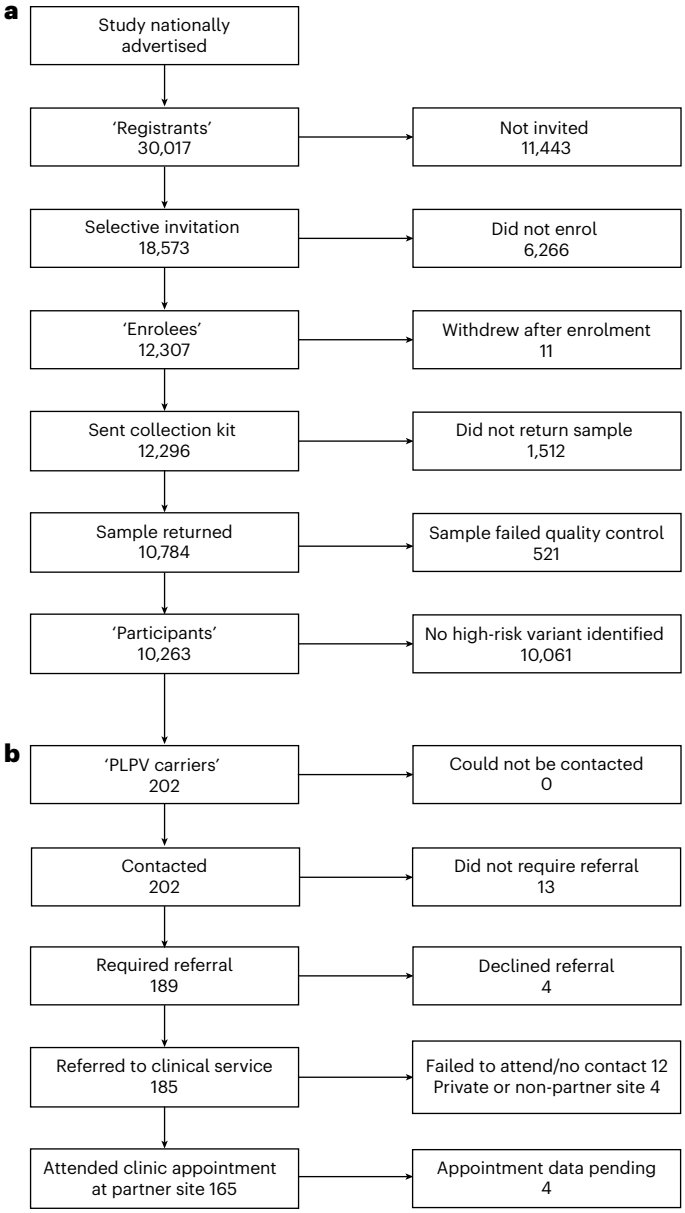

Fig. 1 | Overview of the DNA Screen process. a, Recruitment and enrolment of the study cohort. **b**, Progression of identified high-risk individuals into clinical care.

A summary of the overall study process and clinical workflow is provided in Fig. 1, including the recruitment, informed consent and enrolment processes (Fig. 1a), and the clinical progression of identified high-risk individuals into downstream care (Fig. 1b).

Of the 18,573 registrants invited to enrol in groups of 500–1,000 over a 15-month period, 12,307 completed the informed consent process and were mailed a saliva sample collection kit (for details of the study invitation and enrolment process, see Methods). The study aimed to recruit proportionally from each state and territory of Australia based on population size, with proportional representation from rural and remote areas and targets of at least 45% male, 3.0% Indigenous Australian and 25.0% CALD participants. To achieve these recruitment goals, under-represented subgroups (including men, registrants from remote, regional and socioeconomically disadvantaged areas, CALD registrants and Indigenous Australian registrants) were invited preferentially.

After excluding those who did not return samples (1,512), those who returned samples that failed quality control despite multiple

Table 1 | Baseline characteristics of registrants, enroled participants and carriers of PLPVs

Characteristic	Registrants (at July 2024), *N*=30,017	Enroled participants who completed DNA screening, *N*=10,263	Carriers of PLPVs identified, *N*=202
Sex; no. (%)			
Female	17,907 (59.7)	5,524 (53.8)	114 (56.4)
Male	11,971 (39.9)	4,668 (45.5)	85 (42.1)
Non-binary	139 (0.5)	71 (0.7)	3 (1.5)
Total	30,017	10,263	202
Median age at recruitment (interquartile range); years	33.6 (28.8–37.4)	31.9 (27.0–36.5)	32 (25.5–36.4)
Indigenous Australians; no. (%)	456 (1.5)	223 (2.2)	7 (3.5)
Country of birth; no. (%)			
Australia	19,113 (63.4)	7,759 (75.6)	148 (73.3)
Other	10,904 (36.3)	2,504 (24.4)	54 (26.7)
Language spoken at home; no. (%)			
English	21,640 (72.1)	8,400 (81.8)	166 (82.2)
Other	8,377 (27.9)	1,863 (18.2)	36 (17.8)
CALD; no. (%)	12,694 (42.3)	3,078 (30.0%)	66 (32.7)

attempts (521) and those who withdrew from the study (11), genomic screening was completed for 10,263 participants. The final cohort is described in Table 1 and Fig. 2. Participants were enroled from all Australian states and territories in proportions reflecting the national population distribution, ensuring geographic representation. The median age of the final enroled cohort was 31.9 years, 45.5% of enroled participants were male and 30.0% were CALD, including 24.4% born outside Australia and foreign-born and 18.2% living in households where English was not the primary language. Indigenous Australians comprised 2.2% of the final cohort.

Survey responses

A total of 10,658 surveys were completed after informed consent, corresponding to an 86.7% response rate. Participants reported predominantly positive experiences of the enrolment process, with the following percentages agreeing or strongly agreeing with statements: "being able to join the study was convenient" (89.9%), "the language was easy to understand" (91.8%), "I had enough information" (88.5%), "I am satisfied with my decision to participate" (89.6%), "the frequency of communication was appropriate" (86.1%), "I feel positive about my involvement" (89.9%) and "genetic testing is acceptable to me" (89.4%).

Gene panel sequencing

The average turnaround time from sample receipt to communicating the result was 13.0 weeks. DNA sequencing and variant curation identified PLPVs in 202 participants (2.0%): 159 pathogenic and 43 likely pathogenic (Table 2). For details of all PLPVs, see the Supplementary Information; 113 were unique to one individual and 33 were detected in more than one individual. No individual had more than one detected PLPV. The genes with the highest prevalence of PLPVs were *BRCA2* (63) and *LDLR* (48).

Return of results, referrals and uptake of clinical care

Participants with detected PLPVs received notifications to contact the genetic counselling team, which disclosed the results by telephone and offered referral to one of 11 specialist medical centres (partner sites). The sites comprised clinical genetics services and lipid clinics servicing all states and territories of Australia. Partner sites provided downstream care and enabled risk management, notified patients' general practitioners and recorded personal and family histories. In addition, the sites collected and reported clinical data to the study using standardized forms. This included any first-degree blood relatives affected by the related disease. Clinicians also assessed whether, before enrolment, referred participants would have been eligible for Australian government-funded clinical genetic testing, considering family history beyond first-degree blood relatives.

We successfully contacted all 202 participants with PLPVs. Of those, 189 (93.6%) required referral to clinical genetic services. Thirteen did not require referral as they were already engaged with clinical services or had genetic test results already known from previous clinical genetic testing. Of these 13 individuals, 10 were technically not eligible to enter the study, having had prior genetic testing with positive results for either HBOC, LS or FH and had answered 'no' to the relevant question at enrolment. The other three had clinical results pending at the time of enrolment.

Of the 185 (97.9%) who accepted referrals, 165 (89.2%) attended appointments at clinical genetic services and were recommended evidence-based risk management. Two participants opted for private care and two were referred to clinical sites outside of the study network. Thirteen declined to attend or could not be contacted by clinics despite multiple communication attempts, and three still have appointments pending. The average time from referral to appointment at a partner site was 13.7 weeks. Figure 1b provides an overview of the clinical process. We did not have sufficient statistical power to test for differences in sex, age, genetic condition, CALD or Indigenous status between participants who attended clinical appointments and those who did not.

Testing criteria eligibility

Among the 165 participants attending clinical genetics appointments, 133 (80.0%) were the first in their families to be identified with a PLPV. Another 32 (19.4%) came from a family where at least one relative was known to carry a PLPV identified previously by a clinical genetics service. These individuals, therefore, would have been eligible for Australian Government-funded cascade testing owing to the presence of these known family PLPVs identified previously.

After clinical assessment, 123 of the 165 participants (74.5%) would have been ineligible for any Australian government-funded genetic testing (Fig. 3). Of those who would have qualified for funded testing, only ten (6.1%) would have been eligible for index-case testing owing to personal risk factors (all with variants in an FH gene and a Dutch Lipid Clinic Network Score (DLCNS) of ≥6).

Of the 113 participants with PLPVs associated with cancer predisposition syndromes HBOC and LS, 82 (72.6%) would have been ineligible for funded testing at enrolment, 31 (27.4%) would have been eligible for cascade predictive testing and none would have been eligible for index-case testing owing to their own personal cancer history or other risk factors. Of the 52 individuals with FH PLPVs, 41 (78.8%) would have been ineligible for funded testing, 10 (19.2%) would have been eligible for index case testing based on high DLCNS and 1 (1.9%) would have been eligible for cascade testing owing to a previously identified family PLPV.

Clinical characteristics and family history

Of the 165 participants with PLPVs assessed at clinical genetic services, 88 (53.3%) reported no family history of the related condition in a first-degree blood relative, while 5 (3.0%) were uncertain of their family history. For the 113 participants with HBOC or LS PLPVs, 56 (49.6%) reported no family history of cancer in a first-degree blood relative. For the 52 individuals with FH PLPVs, 32 (61.5%) reported no family history of coronary artery disease in a first-degree blood relative.

Clinical assessment for participants with FH PLPVs revealed that 50 (96.2%) had no personal history or apparent clinical manifestation

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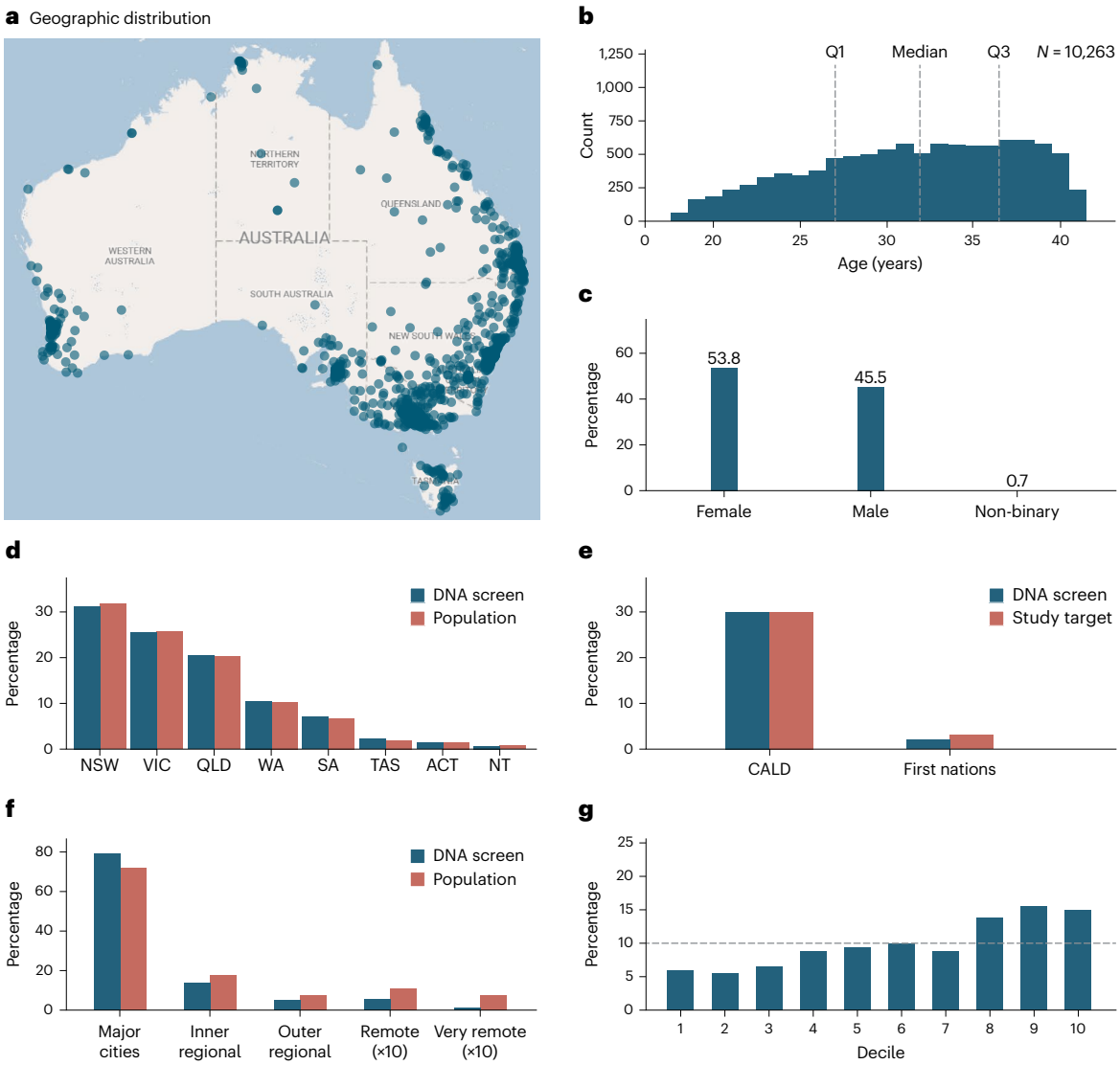

Fig. 2 | Demographic characteristics of the DNA Screen cohort. a, The nationwide geographic distribution of the final enroled cohort (10,263 18–40 year olds). **b**, The age distribution of the final cohort. **c**, The sex distribution of the final cohort. **d**, The state and territory distribution of the final cohort by percentage (blue bars), proportional to expected based on state and territory population sizes (red bars). **e**, The percentage of CALD and First Nations participants in the final cohort (blue bars) versus the study recruitment targets (red bars). **f**, The distribution by geographic remoteness in the final cohort. **g**, The distribution by socioeconomic status (SES) by postcode (with 1 representing the decile with the most SES disadvantage and 10 representing the decile with the least SES disadvantage) in the final cohort.

of coronary artery disease, while one exhibited a high coronary calcium score and another had left anterior descending artery stenosis. Of the 52 participants with FH PLPVs, 20 (38.5%) had not had cholesterol measurements taken in the past year and 33 (63.5%) were not on lipid-lowering medications. Of the 14 participants with cholesterol measures available who were not on lipid-lowering medications, 93% (13) had elevated low-density lipoprotein cholesterol (LDL-C) levels of 100 mg dl^{-1} (2.6 mmol l^{-1}) or higher.

Discussion

This prospective, nationwide study assessed the feasibility of offering population genomic screening for selected high-risk, medically actionable conditions to young adults within Australia's national public healthcare system. The study received a high level of public interest and achieved a high level of clinical engagement, with most individuals with PLPVs attending follow-up clinical appointments. The study provides new evidence regarding the feasibility of adult population genomic screening in a national healthcare system.

Our study advances the field in several ways. The prospective design differs from all previous studies, which have all relied on either retrospective analyses of biobank data, return of secondary findings to pre-existing cohorts, select screening of US state populations or private healthcare networks[2,3,25,27–32]. Our study, by contrast, was prospectively designed de novo to pilot a future population screening programme in line with established public health screening principles. Our study returned primary findings in real time, with a prioritization of feasibility, scalability, clinical utility and timely follow-up. Our study was conducted at a nationwide level, embedded in a national public healthcare system, supporting equitable access and assessment of real-world feasibility across an entire country. Our study focused on young adults, specifically 18–40 years, as guided by our published modelling[22] that indicated this approach would maximize early detection and prevention and yield the greatest benefit in cost-effectiveness and long-term outcomes. This intentional approach was unique and evidence driven, contrasting previous studies that have recruited mostly opportunistically and in predominately older adults.

Table 2 | PLPVs by gene

Condition and gene	Total; no. (% of cohort), *N*=10,263	Pathogenic, no.	Likely pathogenic, no.
Total	202 (1.97)	159	43
HBOC	110 (1.06)	102	8
BRCA1	26 (0.25)	23	3
BRCA2	63 (0.61)	59	4
PALB2	20 (0.19)	19	1
ATM (c7271T>G)	1 (0.01)	1	0
LS	32 (0.31)	19	13
MLH1	4 (0.04)	3	1
MSH2	3 (0.03)	2	1
MSH6	25 (0.24)	14	11
FH	60 (0.58)	38	22
LDLR	47 (0.46)	27	20
APOB	11 (0.11)	11	0
PSCK9	2 (0.02)	0	2

Our study cohort was diverse. Rather than recruit predominately white, older women in a specific limited jurisdiction[2,3,25,27,28], our study recruited a demographically and geographically representative cohort directly from the general population. This was done to simulate a nationwide population screening programme. We achieved high levels of engagement. Our study received >30,000 registrations for 10,000 positions with only one day of advertising, demonstrating the effectiveness of our recruitment approach and high levels of public interest. Of those with PLPVs identified in our study, we observed a high clinical follow-up rate (97.9% of participants eligible for referral accepted, with 87.3% attending clinic appointments).

Our study selectively reported high-risk genes only. Through expert consensus, we excluded moderate-risk genes (for example *PMS2* and *CHEK2*) to avoid risk of overdiagnosis and overburdening of clinical services. We only returned PLPVs where there was strong evidence to support clinical intervention, following established population screening principles. This was done to prioritize clinical utility and overall feasibility of the programme, contrasting other studies where variants in moderate-risk genes have constituted a substantial portion of all reportable results[3,26–28]. Unlike previous studies, including 'In Our DNA SC'[26]—one of the only other published studies with a population-based design—our cohort was more balanced in terms of sex, younger, more diverse, achieved a higher clinical uptake rate and was national in scope (not state level).

Similar to other studies[1–4], however, we had noteworthy consistent findings. The majority of individuals identified with PLPVs in our study, like in other studies, would not have been eligible under current guidelines for funded testing. The current criteria for reimbursed testing in most countries similarly rely heavily on personal and family history of disease and/or the presence of known PLPVs in relatives, and are not designed to identify asymptomatic individuals from the general population. Cascade testing is an exception, offered to asymptomatic family members, but only for the relatively small number of families with PLPVs already identified. Population genomic screening now offers a proactive alternative to the traditional criteria-based testing approach, enabling the early identification of individuals at high risk in the general population who could benefit from preventive care.

Furthermore, consistent with other adult population genomic screening studies[1–3,25,27,29,33], many of the participants identified with PLPVs report no family history of the relevant disease(s). In our study, fewer than half of the participants identified with PLPVs reported a family history. This demonstrates the limitations of using family history to guide genetic testing. A proportion of participants with PLPVs in our study, however, came from families where PLPVs had already been identified clinically (19.5%). Although these participants were eligible for publicly funded cascade testing, we do not know whether they were aware of their eligibility or elected to enrol in the DNA Screen study out of convenience to obtain their genetic results. It is also possible they had concerns about navigating clinical testing pathways, or were interested in broader multicondition testing. Almost all individuals identified with PLPVs in our study (98.1%) had no prior personal diagnosis of a relevant clinical condition, reflecting the younger age range versus prior efforts. This highlights the value of offering population genomic screening before symptom onset, and contrasts with other studies and traditional clinical approaches to genetic testing for the same conditions where diagnosis of disease has often been a prerequisite of funded testing.

The penetrance of PLPVs identified in young individuals from the general population may be lower than that of PLPVs identified in studies of multiple-case families and those identified clinically who meet criteria. For this reason, we intentionally selected only high-risk genes, for which PLPVs are associated with risk of disease that is above clinical intervention thresholds, even after adjusting for ascertainment and family history[36–38]. We included one variant in the *ATM* gene (NM_000051.4:c7271T>G) associated with disease risk equivalent to a high-risk gene PLPV[39]. Clinical risk estimation is a constantly evolving practice and updated gene penetrance data from more prospective population-based studies will further assist future risk estimates.

Our study excluded moderate-risk genes and reporting of variants of uncertain significance. This was done intentionally to minimize downstream ambiguity and healthcare burden. Limiting testing to high-risk genes aligns with population screening principles[11], but needs to be balanced against the trade-off of not identifying individuals at moderate risk who, despite the information given, may have taken false reassurance from their result. In the future, ongoing and careful calibration of gene selection, risk management and healthcare cost will be essential to ensuring benefits outweigh harms in population genomic screening.

The strengths of our study, which provides real-world insights for assessing population genomic screening, include its prospective design; direct public enrolment strategy; accessibility through online, postal and tele-health elements; integration with existing clinical services; and high rate of clinical uptake and follow-up. The study was also intentionally embedded within a national public healthcare system to assess real-world feasibility.

The limitations of the study include its potential for self-selection bias and the invitation of certain registrant subgroups preferentially before others to achieve recruitment goals. Although the cohort was geographically and culturally diverse, definitions of diversity were based on self-reported cultural and linguistic identity[35], not measured genetic ancestry. This was done intentionally to avoid the measurement of genetic ancestry as a requirement of participation. There were technical limitations of the test (for example, the inability to detect large structural variants) meaning that a small subset of PLPVs in the target genes were not detectable. PLPVs identified in the study were research findings that required clinical confirmation through accredited laboratories, arranged by the clinical sites. We acknowledge differences in validation standards, reporting practices and regulatory oversight between research and clinical genetic testing. While the study is prospective (representing an improvement in the level of evidence relative to previous retrospective studies), the current clinical follow-up of our study had a relatively short time horizon, extending only to the first clinic appointment. Longer-term follow-up, including to measure the uptake of clinical interventions and risk-reduction procedures offered, and to quantify impacts on morbidity or mortality attributable to genomic screening, is planned as part of our future research.

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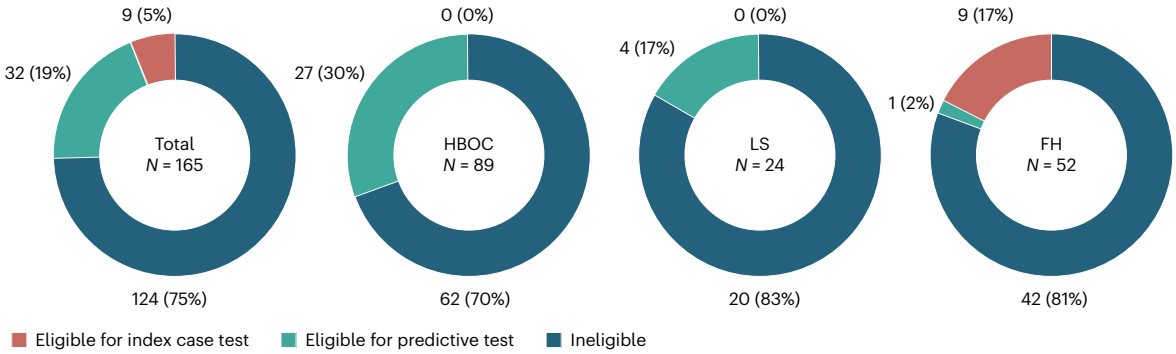

Fig. 3 | Proportion of referred participants eligible for Australian government-funded clinical genetic testing based on current criteria. Results are shown for all conditions combined (total) then separately for HBOC, LS and FH. Participants with identified PLPVs were referred to partner clinical genetic services in the Australian public healthcare system. At the appointments, clinicians at partner sites recorded personal and family histories, and assessed participant eligibility for Australian government-funded clinical genetic testing before enrolment. This included eligibility for either index-case testing or predictive cascade testing. Australian Government reimbursed testing criteria for index cases in Australia vary by condition. Detailed testing criteria are in the Supplementary Information.

Embedding the study within a public healthcare system facilitated screening uptake and follow-up. However, it does not limit the generalizability of our findings, which are of relevance to any large healthcare system considering the implementation of adult population genomic screening. For other countries with national public healthcare systems (for example, the UK, Canada and much of Europe) generalizability is highest. However, there is also generalizability to any other large healthcare system (including the more private or fragmented systems in the USA) that must consider the same practical implementation challenges. These include recruitment and defining of the target population; garnering of public trust; the genomic testing approach used, including gene panel selection; achieving laboratory scale; accounting for workforce needs, including genetic counselling, clinical genetic services and the timely provision of follow-up care; and ensuring the overall cost-effectiveness of the programme (justifying its potential reimbursement). Our study makes fundamental advances in addressing all of the above implementation challenges, which are shared globally.

Other important aspects must also be investigated with further research, including analysis of psychological impacts, further consideration of potential harms and additional health-economic modelling, including to inform the impact of genomic screening in different population target age ranges, genes/variants and conditions groups, and the ongoing budget impact and workforce needs. We have several substudies underway to consider and further develop the evidence base in relation to these matters.

In conclusion, this prospective nationwide pilot has demonstrated the feasibility, high public interest and high clinical uptake of adult population genomic screening in a national healthcare system. Coupled with prior evidence of cost-effectiveness[20,22], the study findings constitute an important component of the broader evidence base now required to inform the future design and possible implementation of a new adult population screening programme in Australia, and any other programme under consideration internationally.

Methods

Participants

On the basis of prior health-economic modelling[20,22], we designed a nationwide pilot study targeting adults aged 18–40 years. The programme was made available to Australian citizens or permanent residents aged 18–40 years with no prior genetic diagnoses of HBOC, LS or FH, and proficiency in English. The design of the programme received input from clinicians, epidemiologists, molecular geneticists, public health experts, health economists, genetic counsellors, communication and education experts and patient organizations. We also worked with a consumer reference group of 12 individuals from diverse backgrounds, including individuals with lived experience of these conditions and one Indigenous Australian. This reference group co-designed and tested materials for the recruitment, registration and informed consent processes.

Our goal was to undertake a prospective study in at least 10,000 individuals from the general population to evaluate the feasibility and referral outcomes of the pilot programme in a diverse national sample. Study recruitment involved two steps: online registration or expression of interest, where volunteers provided basic demographic and contact details (including telephone number and mail address) to become 'registrants'; and formal enrolment, where registrants were invited to view study materials, watch an educational video, complete a knowledge quiz and provide informed consent, becoming 'enrolees'. The informed consent form and participant information sheet are provided in the Supplementary Information. Following enrolment, saliva sample collection kits were mailed, samples were received back from enrolees for DNA testing and the results were returned to all participants. Those with PLPVs identified were offered genetic counselling and referral to clinical services (for an overview, see Fig. 1).

The approach to recruitment was to first promote the study broadly through national media coverage to attract the largest number of registrants possible, then invite registrants in groups over an approximately 15-month period to enrol a nationally diverse cohort. The study recruitment goals were to recruit proportionally from each state and territory based on population size, with a balanced sex ratio. Targets of 3.0% Indigenous Australian participants and 30.0% CALD participants were also set for the final cohort. Diversity was defined using the Australian Bureau of Statistics census definition[35]: country of birth outside Australia or a language other than English spoken at home.

Registrants were invited over 15 months in groups of approximately 500–1,000, with sample batch sizes and timings adjusted to match laboratory capacity and avoid backlogs. Initial groups of invitations reflected national population distribution, with balanced representation by sex, age, state/territory and CALD status. All Aboriginal and Torres Strait Islander registrants, as well as registrants from remote, regional and socioeconomically disadvantaged areas, were invited to enhance representation. Adjustments were made throughout recruitment in response to enrolment patterns, particularly oversampling of men. Towards the end of recruitment, full demographic representativeness was no longer achievable—for example, all eligible men in some states and all eligible participants from regional or remote areas had already been invited.

For generating study invitations, a stratified random sampling process in R (versions 4.2.1 and 4.2.2) was used, with target sample sizes allocated across key demographic attributes to maximize

representativeness within each batch. Those who were invited, enroled and provided informed consent, were asked to complete a survey on participant satisfaction, and were sent saliva sample collection kits (DNA Genotek, ON-600) in returnable postage-paid envelopes.

Genomic screening

Enrolees with samples passing quality control became study participants (Fig. 2). For sequencing quality control thresholds see the Supplementary Information. A custom next-generation sequencing panel (Agilent) was used to detect PLPVs, including single-nucleotide variants and small insertion–deletions in exons of ten genes. We included only high-risk medically actionable genes: *BRCA1*, *BRCA2*, *PALB2* and *ATM* (single high-risk variant NM_000051.4:c7271T>G only) for HBOC; *MLH1*, *MSH2* and *MSH6* for LS; and *LDLR*, *APOB* and *PSCK9* for FH. The assay was validated using PLPV carrier and non-carrier control samples from external studies, performing with 100% concordance. Saliva-derived DNA was extracted, prepared and enriched using SureSelect XTHS2 indexed libraries and sequenced to a target coverage of 200 reads/base (Illumina NextSeq550). The assay was not able to detect large insertion–deletions, copy number variants, structural rearrangements or chromosomal aneuploidy.

Variant analysis

Sequencing reads were aligned to the GRCh38 reference with coding/exon-flanking regions analysed. Variant curation was performed using modified American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) guidelines[40–43]. Benign, likely benign and variants of uncertain significance were not returned, but categorized as a single 'no high-risk variant identified' group. PLPVs were reported to participants after authorization by a clinical geneticist, the laboratory director and principal investigator.

Result disclosure, genetic counselling and referrals

Participants without detected PLPVs each received a research report by email detailing results and test limitations (Supplementary Information). Participants with detected PLPVs each received an email and text notification to contact the genetic counselling team via a toll-free number or online booking system. Genetic counsellors disclosed results by telephone and offered referral to one of 11 specialist medical centres (partner sites) throughout Australia for ongoing management. Partner sites comprised clinical genetics services and lipid clinics with coverage across all states and territories of Australia. Non-responsive participants with PLPVs were telephoned by the genetic counsellors at least three times and sent an email before being considered not contactable.

Clinical data collection and analysis

Each partner site collected and reported clinical data using standardized forms provided by the study (Supplementary Information). Study data were collected and managed using REDCap electronic data capture tool and managed by Helix (Monash University)[44]. Clinicians recorded personal and family histories of referred participants with PLPVs at appointments, including any first-degree blood relatives affected by the related disease. Clinicians also assessed whether, before enrolment, referred participants would have been eligible for Australian Government-funded clinical genetic testing, considering family history beyond first-degree blood relatives. Genetic testing of blood samples through accredited laboratories was undertaken to confirm research results by the clinical sites.

Criteria for Australian Government-funded testing for index cases vary by condition. For HBOC, index cases must have a personal cancer diagnosis and family history meeting ≥10% PLPV probability; for LS, eligibility requires specific cancer histories, diagnostic markers and ≥10% PLPV probability; and for FH, a DLCNS of ≥6 is required. If FH PLPV carriers had LDL-C measures available at the time of genetic results disclosure, these were used to calculate the DLCNS at the first clinical appointment. For FH PLPV carriers without LDL-C measures available, a lipid panel was ordered at the first appointment to calculate the DLCNS, which was then provided to the study thereafter. For details regarding the elevated LDL-C threshold (>100 mg dl^{-1}) see the Supplementary Information. For each condition, cascade testing is available for relatives of confirmed individuals with PLPVs. Detailed criteria are in the Supplementary Information.

Ethics

The DNA Screen study has been approved by the Alfred Hospital Research Ethics Committee (project no. 597/21).

Data analysis

All data analyses were conducted in R (versions 4.2.1–4.4.2).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The primary data from this study are not publicly available owing to restrictions in the informed consent obtained from study participants, which do not allow for public data sharing. De-identified data may be made available from Prof. Lacaze (paul.lacaze@monash.edu) upon reasonable request and following approval by the relevant institutional and ethics committees. Requests will be considered, reviewed and actioned within 6 months of receipt.

Code availability

The code used for participant selection, data processing and analysis can be made available from Prof. Lacaze (paul.lacaze@monash.edu) upon reasonable request and following approval by the relevant institutional and ethics committees. Requests will be considered, reviewed and actioned within 6 months of receipt.

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Author contributions

P.L., J.T., I.W., M.C.S., J.Z., J.J.M., T.N.-D., M.A.Y., K.J.N., D.T., B.T., R.L.M., Z.A., M.B.D. and P.J. designed the study and sought funding. P.L. reviewed the literature, interpreted results and wrote the initial draft of the manuscript. P.L., A.B., T.N.-D., J.S., D.B., A.E.H. and B.A.T. conducted formal analysis. Epidemiological and research expertise were provided by P.L., A.B., J.T., M.C.S., T.N.-D., D.B., F.B., R.L.M., M.-A.Y., A.M.W., L.A.M., K.J.N., B.B., Z.A., R.C.G., R.M. and J.J.M. Clinical expertise was provided by J.Z., M.-A.Y., A.M.W., L.A.M., M.B.D., D.T., A.E.H., G.F.W., J.P., F.M., N.P., J.K., K.T., L.A., M.W., R.S., N.P., D.S., A.R., S.J.N., R.C.G., R.M., P.J. and I.W. All co-authors provided critique and/or review of the manuscript and contributed to writing final draft. P.L., M.C.S. and I.W. are responsible for the overall content as guarantors.

Competing interests

R.M. declares advisory board membership from Astrazeneca/MSD/EGL/GSK, and research funding from Yorkshire Cancer research, CRUK and Rosetrees trust outside this study. R.C.G. has received compensation for advising Allelica, Atria, Fabric, Genomic Life and Jupiter Genomics; and is a co-founder of Genome Medical and Nurture Genomics. S.N. has received research support from AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Eli Lilly, Esperion, Resverlogix, Novartis, InfraReDx and Sanofi-Regeneron and is a consultant for Amgen, Akcea, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Kowa, Merck, Takeda, Pfizer, Sanofi-Regeneron and Novo Nordisk. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s44360-025-00020-x.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44360-025-00020-x.

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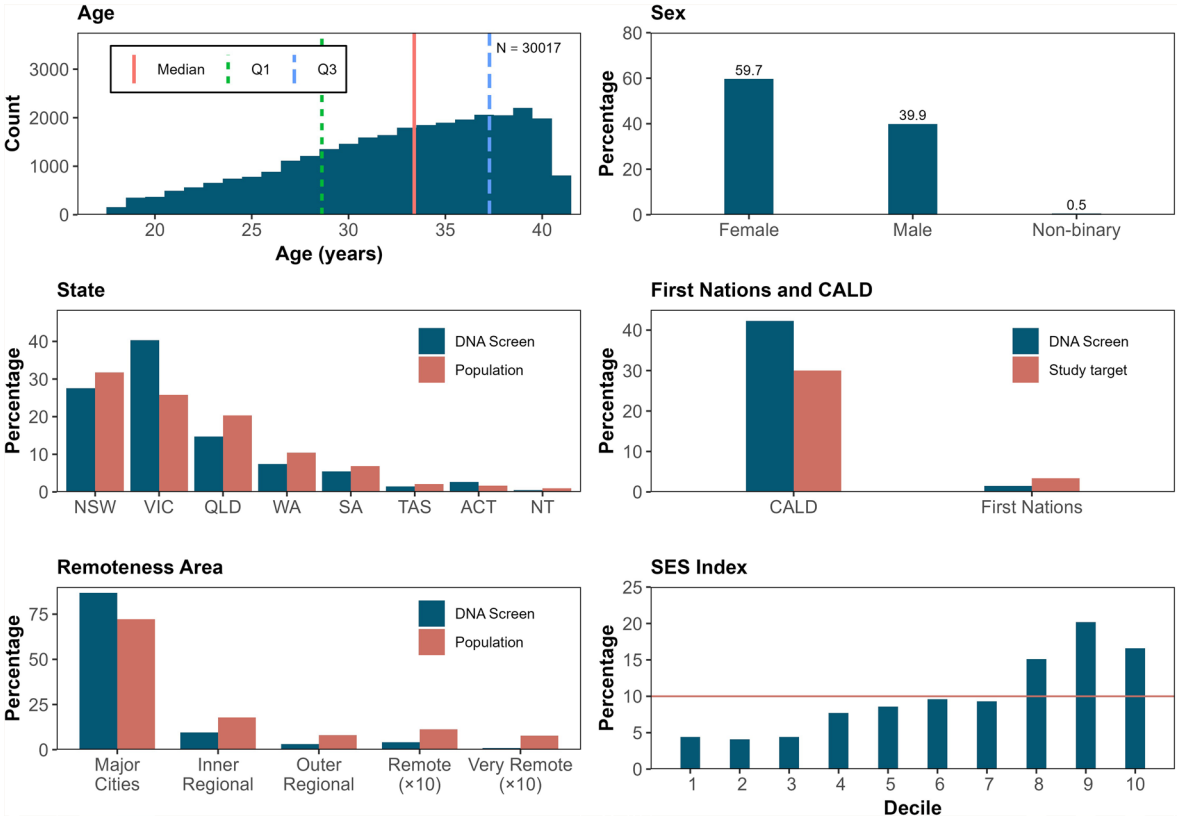

Extended Data Fig. 1 | Demographic characteristics of registrants of the DNA Screen study. Shown is the age distribution of registrants (30,017 18–40 year olds), the sex distribution (59.7% female), the state and territory distribution by percentage (blue bars) proportional to expected based on state and territory population sizes (red bars), the percentage of CALD and First Nations participants (blue bars) versus the study recruitment targets (red bars), the distribution by geographic remoteness, and the distribution by socioeconomic status (SES Index) by postcode, with 1 representing the decile with the most SES disadvantage and 10 representing the decile with the least SES disadvantage.

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☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Study data was collected and managed using REDCap electronic data capture tool.
Data analysis	Variants were called using VarDict software. Study data was analyzed in R.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

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Data Availability

The primary data from this study are not publicly available due to restrictions in the informed consent obtained from study participants, which do not allow for public data sharing. De-identified data may be made available from Prof. Lacaze (paul.lacaze@monash.edu) upon reasonable request and following approval by the relevant institutional and ethics committees. Requests will be considered, reviewed and actioned within 6 months of receipt.

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Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was determined based on self-reporting as either female, male or non-binary. Sex-based analyses were not performed.
Reporting on race, ethnicity, or other socially relevant groupings	The study did not report on race or ethnicity. We instead reported on diversity according to culturally or linguistically diverse (CALD) backgrounds. This was defined, using the Australian Bureau of Statistics census definition, as individuals either born outside of Australia, or speaking a language other than English at home, enabling direct comparison of the cohort's demographic characteristics with national census data.
Population characteristics	10,263 completed genomic screening (median age 31.9 years; 45.5% men; 30.0% culturally or linguistically diverse).
Recruitment	Informed by prior cost-effectiveness modelling, we invited recruitment from young Australian adults aged 18 to 40 years between August 2022 and July 2024, from a nation-wide estimated base population of 8,324,242 individuals. Following 1 day of national media coverage, 30,017 individuals registered to participate—15,899 in the first 48 hours and an additional 4,550 in the first week. Promotion of the study was then discontinued, given the designated target (10,000 participants) had been exceeded. Registration was kept open as a "waiting list", and another 9,568 individuals registered over the following 2 years with no active recruitment.
Ethics oversight	The DNA Screen study has been approved by the Alfred Hospital Research Ethics Committee (Project #597/21).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Our goal was to undertake a prospective study in at least 10,000 individuals from the general population, to evaluate the feasibility and referral outcomes of a pilot adult population DNA screening program in a diverse national sample.
Data exclusions	The program was made available to Australian citizens or permanent residents aged 18 to 40 years with no prior genetic diagnoses of hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia, and proficiency in English.
Replication	n/a (this was a real-world feasibility study)
Randomization	n/a
Blinding	n/a

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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Clinical trial registration	n/a
Study protocol	The DNA Screen study protocol can be accessed by the Alfred Hospital Research Ethics Committee (Project #597/21) or from the corresponding author upon reasonable request.
Data collection	Participants with detected PLPVs received notifications to contact the genetic counselling team, which disclosed results by telephone and offered referral to one of 11 specialist medical centers (partner sites). The sites comprised clinical genetics services and lipid clinics servicing all states and territories of Australia. Partner sites provided downstream care and enabled risk management, notified patients' general practitioners, and recorded personal and family histories. In addition, the sites collected and reported clinical data to the study using standardized forms. This included any first-degree blood relatives affected by the related disease. Clinicians also assessed whether, prior to enrolment, referred participants would have been eligible for Australian Government-funded clinical genetic testing, considering family history beyond first-degree blood relatives.
Outcomes	Clinicians recorded personal and family histories of referred participants with PLPVs at appointments, including any first-degree blood relatives affected by the related disease. Clinicians also assessed whether, prior to enrolment, referred participants would have been eligible for Australian Government-funded clinical genetic testing, considering family history beyond first-degree blood relatives.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*