

*H. sapiens* ancestors. If European fossils – and even African skulls such as those recovered at Bodo in Ethiopia or Kabwe in Zambia<sup>14</sup>, which are frequently regarded as direct ancestors of modern humans – are better placed within the Neanderthal–Denisovan clade, then the following key question emerges<sup>15</sup>. Where are the fossils representing the *H. sapiens* lineage between 700,000 and 300,000 years ago?

Several other questions remain unanswered. The resemblance between the Thomas Quarry I finds and some Middle Pleistocene European fossils is puzzling, particularly regarding characteristics that are considered typical of Neanderthals, such as a distinctive facial feature – when viewed from the side, the back of the jaw does not reach over the third molar, leaving the tooth visible. This raises a wider question. Why would the roots of the lineage that led to *H. sapiens* have Neanderthal-like traits? This is noteworthy because Neanderthal traits should represent specializations that developed after divergence from the *H. sapiens* lineage. Possible explanations include misinterpretations of ancestral traits inherited from early ancestors; cases of parallel evolution in which similar features arose independently; or offspring who had parents of different lineages (through gene flow between late Early Pleistocene populations from both sides of the Mediterranean).

Dental evidence is relevant to the discussion of how deeply the *H. sapiens* and Neanderthal–Denisovan clades diverged. There is a proposal of shape differences between Eurasian and African hominin teeth<sup>16</sup>. The dentition of *H. antecessor* has several characteristics associated with the Eurasian dental pattern, later retained by European Middle Pleistocene populations such as those from the Sima de los Huesos site in Atapuerca, Spain. A variety of these characteristics associated with Neanderthal teeth point to ancient roots for Neanderthal dental patterns. That proposal and the one by Hublin and colleagues both recognize a divergence between African and Eurasian hominin lineages that might date back one million years, if not longer. If interpreted this way, the Eurasian lineage would be closely linked to the Neanderthal–Denisovan clade.

By contrast, Hublin and colleagues anchor the *H. sapiens* lineage firmly within African populations derived from *Homo erectus*, following an evolutionary trajectory that would ultimately lead to modern humans. The extinct species of *H. erectus* arose in Africa about 1.9 million years ago and spread across Eurasia, surviving in southeast Asia until about 100,000 years ago. This conceptual convergence reinforces the idea that human lineages might have been diversified much earlier than previously thought – with implications for the interpretation of shape variations in the fossil record.

As a result of these developments, neither

the fossils attributed to *H. antecessor* nor those recovered from Thomas Quarry I can be viewed as the strict LCA of *H. sapiens* and the Neanderthal–Denisovan clade, but rather they can be considered as closely related lineages positioned near the ancestral node at the onset of new evolutionary specializations. Current interpretations suggest that *H. antecessor* might lie close to the root of the Neanderthal–Denisovan lineage, whereas its North African counterpart might have been associated with the early evolution of *H. sapiens*. The study of human evolution thus remains a dynamic and compelling field, continually reshaped by fossil discoveries and analytical advances.

**Antonio Rosas** is in the Department of Paleobiology, National Museum of Natural Sciences (CSIC), 28006 Madrid, Spain. e-mail: arosas@mncn.csic.es

Health care

# National genetic screening catches disease risk early

Teri A. Manolio

A study in Australia supports genetic screening in young adults before symptoms show, but the generalizability and cost–benefit ratios need to be examined in other settings.

Cancer and cardiovascular disease are leading causes of death in high-income countries. Often, symptoms of these conditions become apparent only in late-middle or older ages, when they have progressed to advanced and potentially irreversible forms. Genetic screening for hereditary breast and ovarian cancer, colorectal cancer and familial hypercholesterolaemia (high cholesterol), as recommended by the US Centers for Disease Control and Prevention<sup>1</sup>, can identify people who are at increased risk of these conditions long before they develop. This enables enhanced screening or treatment to prevent their often devastating consequences. Yet large-scale, population-wide genetic screening remains an unattained goal, with few studies having tested its feasibility and impact outside of selected private health systems. Writing in *Nature Health*, Lacaze *et al.*<sup>2</sup> evaluated the uptake and yield (the number of at-risk individuals identified) of genetic screening among roughly 30,000 adults aged 18–40 years in a prospective nationwide pilot in Australia.

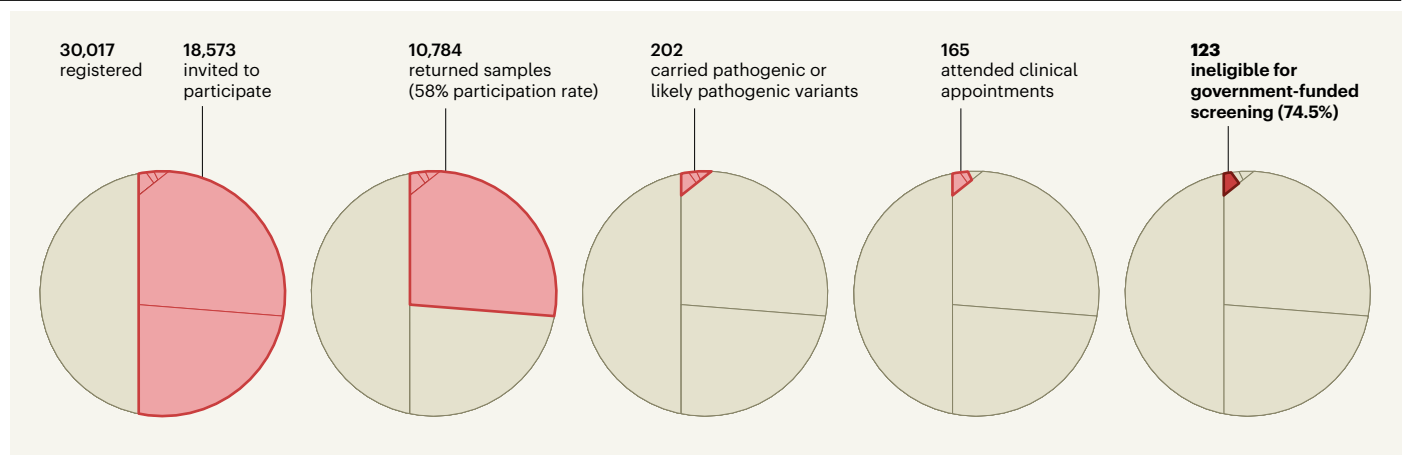
This effort complements previous studies of population genetic screening<sup>3–6</sup> by its extensive efforts to ensure proportionate inclusion

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of major demographic groups in Australia, and its emphasis on engagement with consumers, clinicians and public-health experts to optimize access and uptake. From a pool of 30,017 adults, 18,573 were invited for screening, of whom 10,784 returned samples, giving a participation rate of 58%. Goals for diversity in geography, language and other demographics were largely met and were reflective of the highly diverse population of Australia.

The authors screened for genetic variants that are known to cause disease (‘pathogenic’) or are expected to be disease-causing (‘likely pathogenic’). All of the 202 participants who were found to carry pathogenic or likely pathogenic variants were successfully contacted – an impressive achievement. Of these individuals, 189 met criteria for referral to clinical services, and all but 4 of those accepted a referral. Of the remaining 185, all but 20 attended clinical appointments in the study network, for a successful within-study referral completion of 87%. Of note, 8 of those 20 either attended appointments outside the study or had appointments pending at the time the paper was written, so that the actual referral completion could be as high as 94%. Crucially,



**Figure 1 | Uptake and yield of genetic screening.** Lacaze *et al.*<sup>2</sup> ran a nationwide genetic screening pilot in Australia to identify adults aged 18–40 years who are at risk of developing various diseases later in life. The figure reports the numbers of individuals who: registered for the study; received invitations to participate; completed genetic screening; were identified as carriers of disease-causing (pathogenic) or probable disease-causing (likely pathogenic) genetic variants; and attended clinical appointments within the

study network after a referral. Although the authors successfully contacted all individuals carrying pathogenic or likely pathogenic variants, the moderate participation rate (58%) highlights the difficulty of getting all eligible people to engage in such health interventions. Notably, most (74.5%) of the individuals carrying pathogenic or likely pathogenic variants who attended appointments would not have qualified for government-funded genetic screening according to current criteria.

of the participants who attended within-study appointments, 74.5% would not have met eligibility criteria for genetic testing funded by the Australian government (Fig. 1).

These findings are important because they emphasize the high proportion of at-risk people who are missed by current screening guidelines. For Australia, these guidelines include either receiving a personal diagnosis or having a strong family history of the condition. The goal of preventing disease through genetic screening is thwarted by waiting until a personal diagnosis is made, and family history is often incomplete or not assessed at all in clinical settings.

These results also demonstrate that there is a high acceptance rate of referral among those who provide samples and receive results indicating that they carry pathogenic or likely pathogenic variants. However, the generalizability of these findings outside of Australia's health system and cultural milieu has yet to be demonstrated. The report also provides a clear description of the clinical workflow for such a programme, which could be useful as a road map for related projects. Efforts to include a wide range of individuals were notably successful, although rates of enrolment and sample return among specific subgroups are yet to be reported.

Several caveats apply, however. The 58% participation rate is a sobering reminder of the difficulty of achieving 'universal screening'. This rate would surely be higher if screening was encouraged or mandated by trusted authorities that provide clinical care, rather than as part of a research programme. Comparisons to other clinically recommended screening efforts in Australia (such as those provided by the Australian government) might provide insights into the potential acceptance

of such measures in a non-research, clinical setting. Similarly, the acceptance and yield of efforts to test first-degree relatives of screening participants, which have been notably low in previous 'cascade screening' studies<sup>7,8</sup> despite the practice often being encouraged in guidelines, would be interesting to examine in this health-care setting and cultural context.

Lacaze and colleagues' study involved screening a relatively narrow age range and a limited set of high-risk genes. Although the cost-effectiveness of screening has been shown to be higher when participants are

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younger<sup>9,10</sup>, its value should not be entirely discounted in older adults, who are often more accepting of health-related interventions. Similarly, casting a wider net of risk genes and variants, in addition to the high-risk genes and clearly pathogenic variants screened for in this work, would identify more people who are at increased risk.

However, doing this would also increase the cost and burden on the health-care system, and potentially identify many who would never manifest disease or would succumb to other conditions first. The possibility of increased anxiety and costs for these people would be an important consideration, but it should be weighed against the potential for identifying early asymptomatic cases at older ages. Early detection of chronic diseases with increased screening in older ages is still more

likely to lead to more effective interventions and improved outcomes than attempting to manage late-stage disease.

Further research to refine the appropriate population subgroups and optimal gene and variant lists (which might well be specific to individual populations and health-care systems) can be designed to improve the yield and reduce the burdens of population genetic screening. In the interim, Lacaze *et al.* have made a considerable contribution by demonstrating effective approaches to achieving high public acceptance of genetic screening and its follow-up in a national health-care system. These findings will probably be most relevant to other national health systems, but should be examined in different settings for the lessons they can provide in improving the effectiveness of population genetic screening.

**Teri A. Manolio** is in the Division of Genomic Medicine, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-6908, USA. e-mail: manolio@nih.gov

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