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Hunter–gatherer genomics: evolutionary insights and ethical considerations

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Hunting and gathering societies currently comprise only a small proportion of all human populations. However, the geographic and environmental diversity of modern hunter–gatherer groups, their inherent dependence on ecological resources, and their connection to patterns of behavior and subsistence that represent the vast majority of human history provide opportunities for scientific research to deliver major insights into the evolutionary history of our species. We review recent evolutionary genomic studies of hunter–gatherers, focusing especially on those that identify and functionally characterize phenotypic adaptations to local environments. We also call attention to specific ethical issues that scientists conducting hunter–gatherer genomics research ought to consider, including potential social and economic tensions between traditionally mobile hunter–gatherers and the land ownership-based nation-states by which they are governed, and the implications of genomic-based evidence of long-term evolutionary associations with particular habitats.

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Introduction

Before the advent of agriculture in Southwest Asia ~12,000 years ago, every human society practiced locally adapted forms of hunting and gathering [1]. Using both modern and ancient genomic techniques, research on the global spread of agriculture and agriculturalist populations from multiple independent centers of domestication has uncovered complex, regionally specific histories of admixture and replacement between agriculturalist and hunter–gatherer societies [2–5]. While many hunter–gatherers adopted new domesticates and became agriculturalists [6], and others appear to have been entirely replaced by agricultural migrants from elsewhere [7], approximately 230 hunter–gatherer societies have maintained this lifestyle through the present day, or at least until the very recent past [8]. Extant hunter–gatherer population sizes are now orders of magnitude smaller than their agriculturalist neighbors, but some maintain high levels of genetic diversity compared to agriculturalist populations, reflecting larger ancestral populations [9], and many hunter–gatherer groups have inhabited their distinct local environments for far longer than their agriculturalist neighbors [10,11]. In still other cases, hunter–gatherers have inhabited environments not conducive to intensive agriculture, such as the high arctic. Thus, hunter–gatherers offer an incredible opportunity to study human adaptations to local environments [12].

While the evidence of environment-specific adaptation in hunter–gatherers from genomic studies is a major focus of this review, we also consider and account for the ethical implications of this research. Marginalized by the spread of agricultural and industrialized societies, modern hunter–gatherers have often been confined to liminal environments worldwide, from the Arctic tundra to the rainforests of equatorial Africa and the Australian desert. Because these societies are inherently reliant on a mobile lifestyle to procure their subsistence, many of the world's remaining hunter–gatherers are threatened by the imposition of political boundaries and property rights that severely restrict their ability to access traditional resources. The richness of the hunter–gatherer genetic heritage combined with the exclusion of these societies from many of the formal institutions of the nation-states that control their traditional homelands suggests that they should be considered vulnerable populations by bioethicists and genomic researchers [13–15]. Here we review the recent literature on ethical considerations of genomics research in hunter–gatherer populations. In particular, we focus on issues of informed consent, community engagement, and the culturally and politically sensitive presentation of results from evolutionary genomic studies.

Methods to detect candidate signatures of selection in hunter–gatherer genomes

Recent studies of hunter–gatherer populations have employed generalized scans for positive natural selection to investigate how the varied and often extreme conditions of their local environments may have shaped phenotypic adaptation. Potential signatures of positive selection include unusual shifts in patterns of haplotype variation (i.e., extensive linkage disequilibrium) surrounding a candidate locus, an unusual allele frequency spectrum at a candidate locus, or an unusual degree of between-population allele frequency differentiation relative to the genome-wide distribution for these values [16]. With the increasing feasibility of generating large population genomic datasets, these analytic tools have been used to identify candidate signatures of natural selection in multiple hunter–gatherer populations, as described below.

How do hunter–gatherer adaptations to local environments manifest in the genome?

Among genes located within or nearby genomic loci highlighted by scans for positive selection in worldwide hunter–gatherer populations, several biological pathways recur. First, loci implicated in immune function and parasite suppression appear to have been under strong positive selection (i.e., with signatures of classical selective sweeps on the basis of patterns of haplotype variation, and/or high levels of allele frequency differentiation compared to other populations) in multiple hunter–gatherer populations [17–21]. This finding is not unexpected, given the overrepresentation of immune loci in selection scans in any human population [22,23]. However, compared to agricultural populations, hunter–gatherers experience distinct pathological and parasitological burdens related to significant differences in population density, sedentism, and habitat use. For instance, hunter–gatherer populations in India possess particular variants of the interleukin-4 gene associated with anti-parasitological activity at much higher frequency than their agriculturalist neighbors, possibly as a result of living with higher burdens of helminthic endoparasites [24]. In the Aka, a rainforest hunter–gatherer population from the Congo basin, it has been hypothesized that positive selection has driven to high frequency a genetic variant that confers a reduced efficiency of the CYP2A6 nicotine-processing enzyme, because this phenotype would lengthen the residence time of nicotine in the bloodstream and lower total parasite loads [25].

Other sets of gene ontologies repeatedly overrepresented in scans for positive selection in worldwide hunter–gatherer populations are those involved in metabolism, body mass, and body shape. For example, Siberian and Greenlandic hunter–gatherers appear to have convergently evolved separate metabolic mechanisms for subsisting on a highly carnivorous diet in an extremely cold climate. First, in northeastern Siberia, Chukchi and Koryak populations exhibit one of the strongest selective sweep signatures yet discovered in humans, centered on a functional variant of the long-chain fatty-acid oxidation gene *CPT1A* [26•]. This variant seems to have provided a selective advantage among people with a diet high in animal fats, despite also being associated with increased infant mortality risk due to hypoketotic hypoglycemia [27]. Second, in Greenland, a recent population genomic study of a Greenland Inuit population identified a very strong signature of positive selection on the basis of extreme inter-population allele frequency differentiation near three fatty acid desaturase (*FADS*) genes [28•]. Three SNPs in particular appear to play an outsized role in regulating height and body mass, perhaps related to the adaptive utility of a high body-mass to surface area ratio in the extreme cold of the Arctic, as suggested by Bergmann and Allen's rules [29,30]. Interestingly, the alleles affected by positive selection in the Inuit are also present at low frequencies in non-hunter–gatherer European and East Asian populations, but their associations with height and body mass have been missed in large genome-wide association studies (GWAS) due to their rarity outside of the Greenland population [28•].

Arctic populations are not the only hunter–gatherers who display signatures of body mass evolution. One of the most striking examples of environment-specific human body shape variation is the 'pygmy phenotype,' or small adult body size (e.g., average adult male stature <155 cm), a characteristic common to hunter–gatherer populations inhabiting tropical rainforests in Africa [20] and Asia [19,31,32]. A number of scholars have hypothesized that this phenotype represents an ecological adaptation to the challenging rainforest habitat, potentially providing an evolutionary advantage by reducing metabolic demands in a calorically impoverished environment, easing demands of thermoregulation, improving mobility in the dense undergrowth and for climbing trees, speeding life histories to increase reproductive potential for individual with a high disease burden, or some combination thereof [4,33,34]. Scans for strong positive selection on stature-related loci in rainforest hunter–gatherer populations have suggested that this phenotype may result from independent adaptations on multiple pathways in different populations, including the growth hormone IGF1 pathway [19,20], genes involved in pituitary development and insulin-adiponectin signaling [5], and bone homeostasis and remodeling [17]. In a different approach, Perry *et al.* [35] performed a GWAS to identify 16 genetic loci associated with the pygmy phenotype in BaTwa rainforest hunter–gatherers from Uganda, and then identified a signature of polygenic adaptation (a distributed signature of positive selection) at these loci.

What can these patterns of adaptation tell us about human evolution and variation?

The diverse lifestyles and ecologies of modern hunter–gatherer societies, while changed by interactions with agriculturalists over the past 12,000 years, are still substantially more representative of those experienced by humans over the vast majority of our evolutionary history compared to those of modern agricultural societies. Thus, working with these communities offers a major opportunity to test hypotheses about mechanisms and processes of human adaptation to diverse and changing environments, for example in the repeated observations of signatures of natural selection surrounding genes and genetic variants implicated in fatty acid metabolism, pathogen resistance, and body size variation, as discussed above. Of course, there is also value in wider views of human adaptation to local environments, that is, those that consider evolutionary responses to challenging environments in both hunter–gatherer and agriculturalist populations. For example, the evolution of population-specific mechanisms to high altitude habitats along the hypoxia-inducible transcription factor pathway in Andean hunter–gatherers, Ethiopian pastoralists, and Tibetan agriculturalists demonstrates convergence among both genetically and culturally differentiated human populations [36,37].

Results from hunter–gatherer genomic studies also tentatively suggest that when complex traits are under strong directional selection in the context of challenging local environments, we may observe high frequency alleles with larger effect sizes on these traits than have been typically identified via GWAS in agriculturalist populations from developed countries [38]. For instance, a single SNP in a Greenlandic Inuit population was responsible for a per-copy decrease of 0.66–1.2 cm in stature [28•], and multiple pygmy phenotype-associated genomic regions in BaTwa rainforest hunter–gatherers have 2–3 cm effects on stature [35]. Thus, while GWAS cohorts for complex traits in populations with European ancestry are now typically magnitudes larger than those sampled for hunter–gatherer genomics studies [39], the smaller hunter–gatherer studies may still offer novel insight into the genetic basis of these traits in humans [12]. Given the sample size and replication disparities between the GWAS conducted to date between hunter–gatherer and agriculturalist populations, further assessment is needed. If this hypothesis is substantiated, then models of the evolutionary histories of complex traits in pre-agricultural human and hominin populations should not be based solely on effect size distributions from the largest GWAS conducted with agriculturalist population samples.

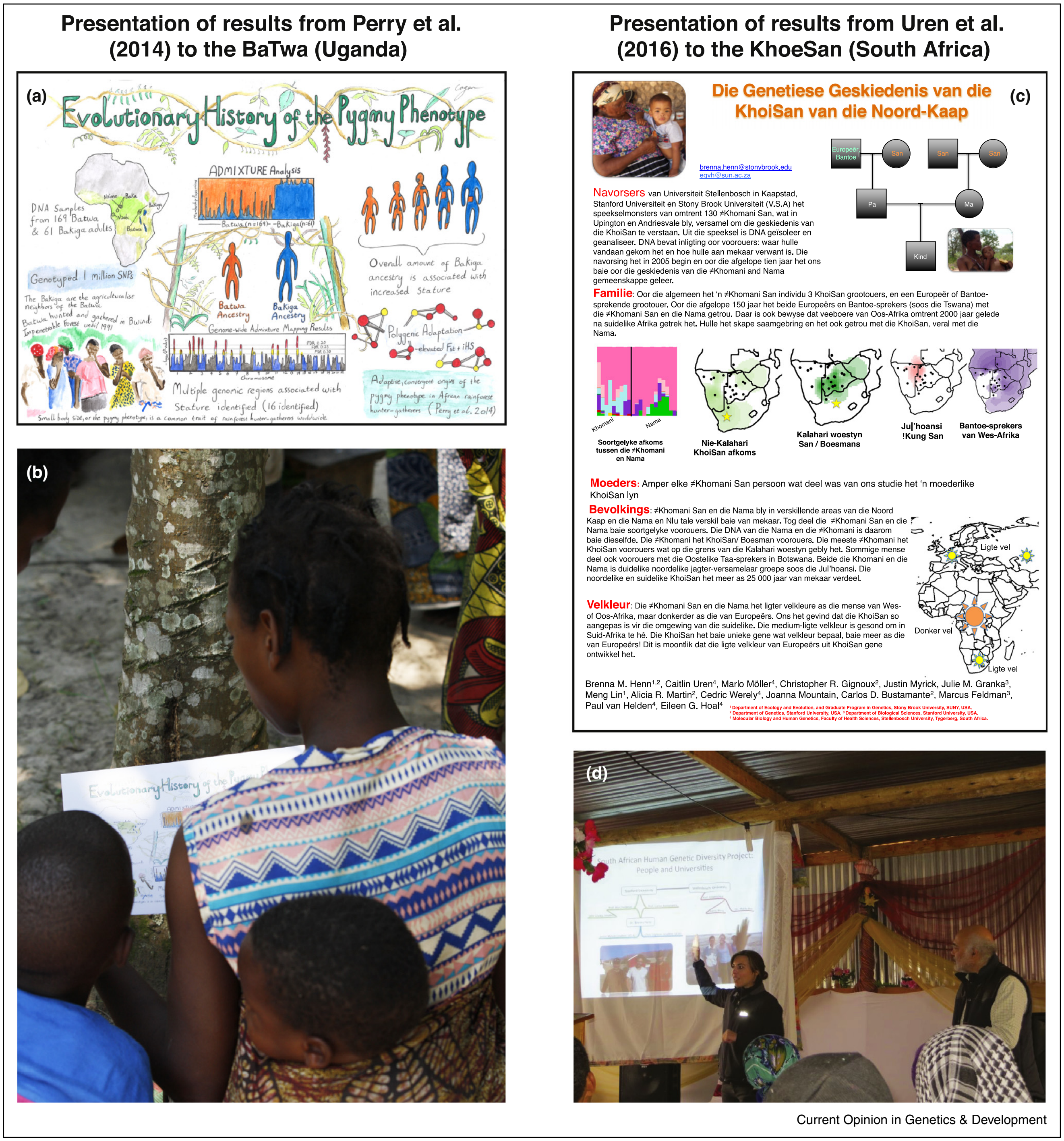
What special ethical concerns arise for hunter–gatherer genomic studies?

As described above, hunter–gatherer genomic research offers the opportunity (along with other insights not discussed) to glean important information about human evolution; however, conducting research with these populations also raises a number of ethical issues for researchers to consider. International, national, and institutional regulatory bodies have established guidelines for the ethical conduct of human subjects research [40,41] and obtaining informed consent from participants. These protections are especially important for populations designated as vulnerable, usually defined as those at heightened risk of harm, exploitation, and limited capacity for consent and/or autonomy [14]. The vulnerability of hunter–gatherers in the context of globalization, development, and conservation policy pressures placed on the ecological integrity of their homelands, and the economic and political fragility of their lifestyles within agriculturalist nation-states, necessitates additional ethical considerations by researchers when studying these populations [42]. We discuss two broad, interconnected categories of specific ethical import for genomics research with hunter–gathers. Firstly, the complexities of obtaining consent in this context, and secondly, the potential issues involved in communicating results to both the subjects and the wider world in both culturally sensitive and politically sensitive manners.

Rates of formal education and literacy are often low in hunter–gatherer societies — of course nearly by definition among members of groups with actively mobile lifestyles. Hunter–gatherers are often further economically and socially disadvantaged as a result of their mobility and tenuous or nonexistent connections to national political and social institutions. Most hunter–gatherer languages do not contain the words for ‘science’ or ‘research’; indeed, in a number of languages, these words are collapsed into a single word synonymous with ‘medicine’, a potentially dangerous conflation for providing informed consent in the context of genomic research [42]. Thus, it is especially important that in addition to written documentation, consent is obtained through a thorough verbal consultation in the native language of the subject [43•], and that the research team partners with any community-based organizations in a best effort to learn how to effectively convey scientific concepts and the potential implications of the research.

Moreover, while willingness may seem an obvious prerequisite for consent, individuals within hunter–gatherer groups may implicitly view their participation as a communal exercise rather than a personal decision [44], a stance that runs counter to the individualistic approach favored by modern research ethics guidelines for informed consent [42]. Alternatively, inter-communal and intra-communal tensions can be aggravated if the prospect of a monetary or other economic reward is attached to participation, even at relatively low levels of compensation [45]. Hunter–gatherers often exist at the margins of nation-states, but they still participate as laborers in national and even international market economies to a greater or lesser degree in order to acquire otherwise unavailable commodities and consumer goods [45]. Other, less obvious economic and political tensions must also be considered. For instance, members of 30 indigenous populations across 11 African countries

Figure 1



Die Genetiese Geskiedenis van die KhoiSan van die Noord-Kaap

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Navorsers van Universiteit Stellenbosch in Kaapstad, Stanford Universiteit en Stony Brook Universiteit (V.S.A) het speekselmonsters van omtrent 130 ≠Khomani San, wat in Upington en Andriesvale bly, versamel om die geskiedenis van die KhoiSan te verstaan. Uit die speeksel is DNA geïsoleer en geanaliseer. DNA bevat inligting oor voorouers: waar hulle vandaan gekom het en hoe hulle aan mekaar verwant is. Die navorsing het in 2005 begin en oor die afgelope tien jaar het ons baie oor die geskiedenis van die ≠Khomani and Nama gemeenskappe geleer.

Familie: Oor die algemeen het 'n ≠Khomani San individu 3 KhoiSan grootouers, en een Europeër of Bantoe-sprekende grootouer. Oor die afgelope 150 jaar het beide Europeërs en Bantoe-sprekers (soos die Tswana) met die ≠Khomani San en die Nama getrou. Daar is ook bewyse dat veeboere van Oos-Afrika omtrent 2000 jaar gelede na suidelike Afrika getrek het. Hulle het skape saamgebring en het ook getrou met die KhoiSan, veral met die Nama.

Moeders: Amper elke ≠Khomani San persoon wat deel was van ons studie het 'n moederlike KhoiSan lyn

Bevolkings: ≠Khomani San en die Nama bly in verskillende areas van die Noord Kaap en die Nama en Nlu tale verskil baie van mekaar. Tog deel die ≠Khomani San en die Nama baie soortgelyke voorouers. Die DNA van die Nama en die ≠Khomani is daarom baie dieselfde. Die ≠Khomani het KhoiSan/ Boesman voorouers. Die meeste ≠Khomani het KhoiSan voorouers wat op die grens van die Kalahari woestyn gebly het. Sommige mense deel ook voorouers met die Oostelike Taa-sprekers in Botswana. Beide die Khomani en die Nama is duidelike noordelike jagter-versamelaar groepe soos die Jul'hoansi. Die noordelike en suidelike KhoiSan het meer as 25 000 jaar van mekaar verdeel.

Velkleur: Die ≠Khomani San en die Nama het ligter velkleure as die mense van Wes- of Oos-Afrika, maar donkerder as die van Europeërs. Ons het gevind dat die KhoiSan so aangepas is vir die omgewing van die suidelike. Die medium-ligte velkleur is gesond om in Suid-Afrika te hê. Die KhoiSan het baie unieke gene wat velkleur bepaal, baie meer as die van Europeërs! Dit is moontlik dat die ligte velkleur van Europeërs uit KhoiSan gene ontwikkel het.

Brenna M. Henn[1,2], Caitlin Uren[4], Marlo Möller[4], Christopher R. Gignoux[2], Justin Myrick, Julie M. Granka[3], Meng Lin[1], Alicia R. Martin[2], Cedric Werely[4], Joanna Mountain, Carlos D. Bustamante[2], Marcus Feldman[3], Paul van Helden[4], Eileen G. Hoal[4]

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Examples of the dissemination of results from hunter–gatherer genomics studies to participant communities. **(a)** Artwork by Alex Cagan to illustrate results from a population genomics study by Perry *et al.* [35] of BaTwa hunter–gatherers from Uganda. **(b)** Batwa woman and child reviewing a printed copy of the poster during a presentation by genomics researchers George Perry and Luis Barreiro. **(c)** Poster in Afrikaans distributed in participant communities to highlight results from a population genomics study by Uren *et al.* [60] of KhoeSan hunter–gatherers and pastoralists from South Africa. **(d)** Genomics researchers Brenna Henn, Stony Brook University, and Cedric Werely, Stellenbosch University, presenting study results to the Khomani San community [foreground].

independently described a fear that genetic variants associated with particular communities might tarnish the perception of the ethnicities in which they were discovered, throwing up significant barriers to economic and marriage opportunities with other groups [46].

Adding to anxieties about harmful interpretations of genomic data, a number of projects around the world have targeted hunter–gatherer and other indigenous groups for biobanking, genomic sampling, and other genetic research over the past decade, many touting the possibility of improved healthcare outcomes [47–49]. While building such datasets is necessary to further medical and human evolutionary genomics research, data generated by genomics studies are often stored indefinitely in publically accessible databases, and can be put to uses not initially foreseen or consented to by the subjects from whom it was initially gathered [50]. This could be particularly concerning when the subjects are hunter–gatherers who are unlikely to discover, much less protest, potential misuses [47,51]. Issues along these lines should be limited by partnership and thorough communication from the outset of any research, as discussed below.

Genomics research may also have implications for the vulnerable political status of hunter–gatherer groups. Many hunter–gatherers live in environments increasingly encroached upon by extractive industries and conservation zones managed by remote governments that may be indifferent to their plights [52,53]. Studies that identify an evolutionary ecology association between hunter–gatherers and a particular geographic region or landscape could increase tensions between these communities and governments and corporations seeking to impose conservation and development strategies that would partition the landscape [54]. Alternatively, findings that rather reveal or imply a short history of occupation in a particular landscape or lifestyle could theoretically enable the political disenfranchisement of a legitimate group that would otherwise be afforded the opportunity for self-determination [55]. Either of these outcomes could have indirect effects on forced settlement or relocation proceedings, an increasingly common policy toward hunter–gatherers in the developing world, and one that usually leads to impoverishment and poor health outcomes [56,57]. Researchers should therefore be especially sensitive to local political and historical contexts. In some cases, this may mean that certain analyses should be forgone altogether to prevent unintended negative repercussions.

Negative outcomes such as those discussed above can be limited by working with participant communities from the very first stages of project design to outline potential areas of conflict on the basis of a discussion of a range of possible results from the study. In addition to preventing unintended consequences, collaborative approaches that emphasize community partnerships and education have the potential to hold the interest of participants far beyond the duration of fieldwork [58]. A study on genetic risk factors for metabolic disease in Aboriginal Australians and Torres Strait Islanders is an exemplar of this strategy [59]. Researchers met with elders and parents of the community, presented their proposed research at open town-hall style meetings, and received feedback on their proposed research questions, leading to a comprehensive memorandum of understanding covering topics from research design to the dissemination of results.

Finally, we and others strongly advocate for the presentation of results from genomic research studies to the participant communities [15,44,58] (Figure 1). As necessary, funds for return visits to the participant communities should be budgeted into grant proposals, and agencies that fund human subjects research should also have this expectation.

Conclusion

Signals of localized evolution detected in modern hunter–gatherer populations have highlighted functional mechanisms of adaptation at work in humans, extending from the distant past through the present. While this rich genetic heritage presents invaluable opportunities to explore the breadth of variation present in the modern human gene pool, the often vulnerable economic and social positions of hunter–gatherer societies requires that researchers are especially conscientious of their subjects' social context throughout study design, implementation, and interpretation. By combining an awareness of potential ethical, social, and economic pitfalls with a commitment to community engagement and the sensitive and thorough communication of results, we will be most likely to achieve a positive outcome for all relevant stakeholders.

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