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Diversity in a dish: Leveraging organoids to reflect genetic ancestry and sex differences in health and disease

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The interplay between genetic ancestry and biological sex is increasingly recognized as a critical factor influencing health outcomes, treatment efficacy, and drug toxicity. Current research highlights significant disparities in disease susceptibility and therapeutic responses across different ancestral groups and sexes, with underrepresentation of diverse populations in genomic studies impeding progress. Most Genome-Wide Association Studies (GWAS) remain predominantly European, hindering the development of accurate polygenic risk scores (PRS). Additionally, sex-related differences in drug metabolism, immune response, and disease prevalence necessitate sex-stratified analyses. This review underscores the potential of advanced *in vitro* models, particularly human pluripotent stem cells (hPSCs) and adult stem cell-derived organoids, to bridge these gaps by providing platforms that reflect human genetic diversity and facilitate high-throughput screening. By integrating diverse genetic data and leveraging donor/population-specific organoid models' researchers can uncover critical genotype-phenotype associations that enhance understanding of health disparities and improve pharmacogenomic applications. To increase reproducibility and throughput, standardized protocols, implementing automation, and employing organoid arrays along with well-controlled pooled populations can streamline workflows and enhance repeatability across studies and geographies. This approach fosters personalized medicine aimed at optimizing treatment efficacy and reducing adverse reactions across diverse populations, promoting equitable healthcare outcomes.

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The role of genetic diversity in human health and disease

Variability in health outcomes, treatment efficacy, and toxicity is increasingly understood to stem from the intricate interplay of genetic ancestry and biological sex [1–3]. Despite significant progress in clinical and genomic research, the underlying mechanisms driving health disparities remain poorly understood, primarily due to the limited diversity represented in genetic studies [4]. For instance, trans-ancestry studies are vital for understanding conditions like cystic fibrosis, where the ΔF508 mutation accounts for 70 % of cases in individuals of Caucasian descent but less than 30 % in those of African ancestry [5]. Similarly, the V122I mutation in transthyretin amyloid cardiomyopathy predominantly affects individuals of African ancestry [6]. Numerous clinical studies have documented striking inter-ethnic and inter-sex differences in disease prevalence, as summarized in Table 1.

Although nearly half of Genome-Wide Association Studies (GWAS) now include non-European participants, an alarming 79 % of the samples still originate from individuals of European ancestry, leaving African, Hispanic, Middle Eastern and Asian populations significantly underrepresented [7,8]. This lack of diversity poses a considerable barrier to fine-mapping genetic loci and developing effective polygenic risk scores (PRS), which are crucial for addressing health disparities in pharmacogenomics [9]. These disparities manifest in pronounced differences in drug metabolism and efficacy among various population groups [10]. For instance, sub-Saharan African populations metabolize clozapine more rapidly than their European counterparts, while East and Southwest Asian populations are generally slower

Table 1

Disease prevalence variations across genetic ancestry and sex.

Disease	Genetic Ancestry Differences	Sex Differences	References
Alzheimer's Disease (AD)	Higher prevalance in individuals of Caucasian ancestry.	More common in women, possibly due to longevity and hormonal factors.	PMID: 9508150 PMID: 37396653 PMID: 37357285
Asthma	Higher prevalance in individuals of Caucasian ancestry.	In the USA, more prevalent in females than males.	PMID: 35662525 PMID: 35150902 PMID: 38580691
Breast Cancer	Higher prevalence in individuals of African ancestry.	More common in women, but men with BRCA mutations are also at risk.	PMID: 38572751 PMID: 19241424 PMID: 38339330
Atherosclerotic Cardiovascular Disease (ASCVD)	Higher prevalence in African and South Asian populations.	More common in men earlier in life; risk increases in women post-menopause.	PMID: 36376533 PMID: 33592281
Cystic Fibrosis	Higher prevalence in individuals of Caucasian ancestry.	No significant sex differences.	PMID: 39307666 PMID: 11713719 PMID: 37244841
Duchenne muscular dystrophy (DMD)	Higher prevalence in individuals of Caucasian ancestry; new variants are being reported in Africa.	More common in males, but female carriers may show mild symptoms.	PMID: 29698937 PMID: 25604253
Huntington disease-like 2 (HDL2)	Only reported in patients with definite or probable African ancestry.	N/A	PMID: 38114648
Hypertension	Higher prevalence in individuals of African ancestry.	More common in men before age 55; prevalence increases in women after menopause.	PMID: 22427070 PMID: 34365809
Inherited retinal dystrophy (IRD)	Higher prevalence in African populations.	Males are more genetically susceptible due to X-linked genes.	PMID: 38519591
Lassa fever (LF)	Endemic to West Africa.	Higher positivity rates in males, likely due to occupational exposures.	PMID: 38326571 PMID: 37085507
Lung Cancer	Higher incidence in African American ancestry.	More common in men, but women may develop cancer earlier and with less tobacco exposure.	PMID: 21964005 PMID: 37537259
Multiple Sclerosis (MS)	Higher prevalence in individuals of European ancestry.	More common in women (2–3 times) than in men.	PMID: 37184850
Osteoporosis	Higher prevalence in Caucasians and Asians than African Americans.	More common in women, especially post-menopause due to estrogen loss.	PMID: 37301857 PMID: 38090417
Parkinson's Disease	Higher prevalence in individuals of Caucasian ancestry.	More common in men.	PMID: 31868680 PMID: 36699001
Prostate Cancer	Higher prevalence in African ancestry individuals.	N/A	PMID: 36066378
Sickle Cell Disease	Primarily affects individuals of African, Mediterranean, Middle Eastern, and Indian ancestry.	No significant sex differences.	PMID: 21546286
Spinocerebellar ataxias (SCAs)	Higher prevalence in individuals of European ancestry in North America.	No significant sex differences	PMID: 26003224 PMID: 31538086
Systemic Lupus Erythematosus (SLE)	Higher prevalence in African American, Afro-Caribbean, and South Asian populations compared to Caucasians.	More common in women (9–10 times) than in men.	PMID: 38057256 PMID: 20063186 PMID: 27940583
Type 2 Diabetes	More prevalent in African American, Hispanic, and Native American populations.	No significant sex differences.	PMID: 22438884 PMID: 36897358

N/A = Not Available (data not reported or assessed).

metabolizers, necessitating tailored dosing regimens for these ancestral groups [11]. Moreover, broad descriptors such as "African" or "Asian" can be misleading, as they fail to capture the remarkable genetic diversity within these populations [12,69]. For example, significant differences exist between Tsonga and Xhosa-speaking individuals in the prevalence of glucose-6-phosphate dehydrogenase (G6PD) allele variants, resulting in notably different risk profiles for chloroquine efficacy within a single African country [13].

The human leukocyte antigen (HLA) system, one of the most polymorphic regions in the human genome, plays a central role in immune surveillance by presenting antigens to T cells. Its diversity reflects the combined effects of ancestry, genetic drift, admixture, and evolutionary pressures such as balancing selection and pathogen exposure. HLA allele frequencies vary markedly across populations—e.g. *HLA-B15:02* is common in Southeast Asians but rare in Europeans—highlighting the impact of local adaptation and demographic history [14]. These population-specific patterns of variation have major clinical implications, particularly in pharmacogenomics. Well-characterized variants in both HLA and drug-metabolizing enzymes and transporters (DMET genes), such as *CYP2D6* or *SLCO1B1*, differ significantly in frequency across populations [2,15]. Established associations between specific genetic polymorphisms and adverse drug reactions (ADRs)—such as *HLA-B57:01* with abacavir hypersensitivity (rare in African populations) [16,17], *HLA-B15:02* with carbamazepine-induced toxicity in South East Asians [18], and *CYP2C19* loss-of-function alleles with clopidogrel resistance—highlight the importance of considering population variation in clinical decision-making (Table 2). These genotype frequency differences are well documented both between and within populations and critical for advancing precision medicine, improving transplant compatibility, and reducing ADRs globally [19].

Breast cancer research further illustrates the impact of pharmacogenomic variation across populations. Genetic differences in key drug-metabolizing enzymes such as *CYP2A6* and *CYP2D6*, which metabolize chemotherapy drugs, contribute to variability in treatment outcomes among Caucasian American, African American, and Asian American women [20]. Difference in genes involved in xenobiotic metabolism can significantly affect both the efficacy and safety of therapies. A notable example is *CYP2C19*, which catalyzes the bioactivation of the antiplatelet prodrug clopidogrel. Variations in *CYP2C19* genotypes are distributed unevenly across ethnic groups, affect the formation of clopidogrel's active metabolite. Patients who are intermediate and poor metabolizers may have reduced platelet inhibition and increased risk of major adverse cardiovascular and cerebrovascular events, reinforcing the need for genotype-guided strategies in antiplatelet therapy [21].

Unfortunately, the underrepresentation of diverse populations in pharmacogenomic research has contributed to inaccurate risk prediction models and increased ADRs in these groups. For example, polygenic risk scores (PRS) for schizophrenia have been shown to overestimate risk in African populations by a factor of ten [7,22]. Efforts to improve representation, such as trans-ancestry meta-analysis in Japanese populations that identified 43 novel loci and improved PRS performance, demonstrate the potential of inclusive research frameworks [23].

In addition to ancestry, sex differences also play a critical role in shaping health outcomes, immune responses and drug metabolism. Women typically exhibit stronger immune responses, which contribute to a higher prevalence of autoimmune diseases and a more robust protection against viral infections, such as HIV and Hepatitis C, compared to men [24]. However, this immune dysregulation may increase risk for conditions like atherosclerotic cardiovascular disease (ASCVD), where traditional risk scores often underestimate risk in women - especially those with immune-related comorbidities [24]. Furthermore, sex hormones influence pharmacokinetics by modulating drug absorption, distribution, metabolism, and excretion across lifespan [25]. For example, genetic variants affecting opioid metabolism can lead to more frequent and severe ADRs in women, highlighting the need for sex-stratified clinical analyses [26]. The historical underrepresentation of women in clinical trials has amplified these disparities. Women account for approximately twice as many ADR reports as men, due in part to differences in drug metabolism and hormone interactions [27]. For example, early findings from the Women's Health Initiative (WHI) suggested that hormone replacement therapy lowered cardiovascular risk. However, subsequent data revealed an increased risk in women, highlighting the dangers of extrapolating results from male-dominated studies [28,29]. According to the U.S. Government Accountability Office (GAO), four of ten drugs withdrawn between 1997 and 2001 were removed due to significantly higher adverse events in women. These included severe cardiovascular and hepatic toxicities, which likely stemmed from sex-specific metabolic differences and clinical underrepresentation [30].

Similar concerns apply to racially biased algorithms in dosing. For example, warfarin dosing models based on European populations have been shown to increase bleeding risk in African American patients due to differences in genes affecting metabolism [31]. These examples underscore the urgent need for inclusive, biologically relevant preclinical models that reflect both population and sex diversity. Table 2 summarizes susceptibility to ADRs reactions across these variables.

Organoids as platforms for investigating ancestry and sex-specific differences

To address these disparities, next generation *in vitro* systems such as organoids offer a promising solution (Figure 1). Organoids provide physiologically relevant, three-dimensional (3D) models that better replicate human tissue architecture than traditional two-dimensional cultures. Derived from renewable sources

Table 2

Factors influencing adverse drug reaction susceptibility: Population genetics and sex differences.

Drug	Clinical Use	Adverse Drug Reactions (ADRs)	Population-Specific Genetic Factors	Sex-Associated Differences	References
Abacavir	Treatment of human immunodeficiency virus (HIV) infection	Abacavir hypersensitivity reaction	Hypersensitivity to abacavir is strongly associated with the presence of HLA-B57:01. This allele's frequency varies across populations, being less common in individuals of African ancestry. Studies show a lower incidence of abacavir hypersensitivity among African children, likely due to lower prevalence of HLA-B57:01 in these populations. Genetic screening for HLA-B*57:01 is a recommended strategy to reduce risk.	No sex-related differences in hypersensitivity reactions; response to therapy appears similar.	PMID: 28092143 PMID: 28315856 PMID: 28424561 PMID: 21164384 PMID: 26738811
Acetaminophen (Paracetamol)	Pain and fever reduction	Hepatotoxicity (at high doses)	Increased susceptibility to acetaminophen-induced liver injury in Caucasian populations compared to Chinese populations, likely due to the presence of low metabolizing variants CYP2E1 and CYP2D6.	No known sex-associated differences reported.	PMID: 27350943
ACE Inhibitors & β-blockers	Hypertension	Angioedema	Higher risk of angioedema in individuals of African ancestry compared to European and Asian populations. Functional polymorphisms in the ACE gene may account for response to ACE inhibitor therapy.	Greater risk reported in females.	PMID: 30296897 PMID: 19659669
Carbamazepine (CBZ)	Seizures and neuropathic pain	Stevens-Johnson syndrome, toxic epidermal necrolysis, maculopapular rash	Hypersensitivity reactions to CBZ are strongly associated with HLA alleles: HLA-B15:02 (Southeast Asian), HLA-A31:01 (European, North American, Japanese, and Mexican mestizo), HLA-B58:01 (Han Chinese, Thai, Indian), HLA-A24:02 (Korean).	Some evidence suggests women may experience a higher incidence of cutaneous adverse reactions, though findings are not consistent across all studies.	PMID: 28520367 PMID: 28315856
Clopidogrel	Antiplatelet therapy for cardiovascular disease	Increased bleeding risk	Bleeding risk varies across populations, with higher incidence in African American and Asian patients, and increased intracranial hemorrhage in Hispanic patients. Genetic polymorphisms, particularly in the CYP2C19 gene, influence clopidogrel metabolism and efficacy. The CYP2C19*17 allele, associated with increased	No significant differences observed.	PMID: 30296897 PMID: 35480401 PMID: 19909874

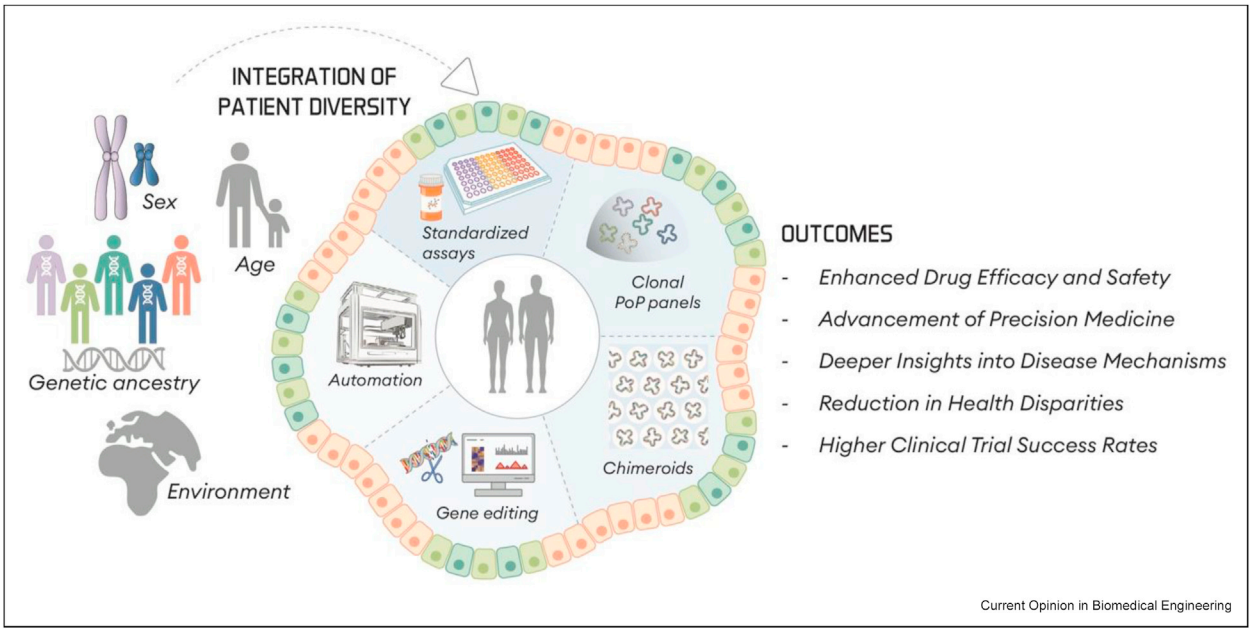
			enzyme activity, leads to a heightened antiplatelet effect and an elevated bleeding risk. The frequency of this allele varies across populations, potentially contributing to observed differences in bleeding incidence.		
Docetaxel	Prostate and breast cancers	Neutropenia, fatigue	East Asian patients have shown increased susceptibility to chemotherapy-induced neutropenia with docetaxel, compared to Caucasian patients. Genetic polymorphisms in drug metabolism and transport genes, such as CYP3A4 and ABCB1, may contribute to these differences.	Female patients may have a higher risk of chemotherapy-induced toxicities, including neutropenia, potentially due to sex-related differences in pharmacokinetics and pharmacodynamics.	PMID: 22095245 PMID: 35884386
Efavirenz (EFV)	HIV treatment	Central nervous system toxicity and neuropsychiatric effects	CYP2B6 polymorphisms, especially CYP2B6*6, affect EFV metabolism, leading to increased plasma levels and CNS side effects. CYP2B6*6 is more common in African and Asian populations compared to Europeans. This genetic variability contributes to inter-individual and inter-population differences in EFV-related neurotoxicity.	Sex does not significantly influence EFV plasma concentrations or CNS-related adverse effects.	PMID: 26288843 PMID: 26779253 PMID: 29633302 PMID: 16267739
Isoniazid	Tuberculosis treatment	Hepatitis, drug-induced liver injury	N-acetyltransferase 2 (NAT2) slow acetylator genotype increases risk of isoniazid-induced hepatotoxicity, particularly in West Asian populations.	Female sex is independently associated with an increased risk of discontinuing isoniazid due to adverse effects.	PMID: 30047605 PMID: 23845828
Levodopa	Parkinson's disease	Levodopa-induced dyskinesia (LID)	Limited population-specific data available; however, polymorphisms in dopamine pathway genes (e.g., COMT, DRD2) may contribute to interindividual variability in Levodopa response.	Higher risk of LID in females, potentially due to hormonal and pharmacokinetic differences.	PMID: 15824260 PMID: 30480086 PMID: 37652906
Platinum-Based Chemotherapy (Cisplatin, Carboplatin, Oxaliplatin)	Head and neck cancers	Nephrotoxicity, ototoxicity	African American race identified as a significant risk factor for cisplatin-associated acute kidney injury (AKI), with significantly increased odds compared to other groups.	No significant differences observed.	PMID: 26556481
Serotonin reuptake inhibitors (SRI)	Mental and behavioural disorders	Depression, and suicide; ineffective	Polymorphisms in CYP2D6, CYP2C19, CYP2B6, and SLC6A4 influence SRI response. The CYP2D617 variant (reduced	ADRs are reported more frequently in women than in men, possibly due to hormonal, metabolitc or	PMID: 37032427 PMID: 29325499 PMID: 29484612 PMID: 11372584

(*continued on next page*)

Table 2. (*continued*)

Drug	Clinical Use	Adverse Drug Reactions (ADRs)	Population-Specific Genetic Factors	Sex-Associated Differences	References
			activity) is prevalent in Bantu-speaking Africans; CYP2C19 shows unique haplotypes in African populations. Additionally, CYP2D6 displays widely variable nonfunctional alleles across sub-Saharan Africa.	hormonal influences, and body composition differences.	PMID: 37929326 PMID: 36111505
Statins (Simvastatin)	Cholesterol reduction	Myopathy, hepatotoxicity	*SLCO1B1 c.521T > C variant linked to statin-induced myopathy. c.521C allele is more common in Asians, contributing to higher risk of ADRs.*	Female sex is a risk factor for statin-induced myopathy; possibly due to hormonal and muscular differences.	PMID: 37818163 PMID: 35848895 PMID: 27484241
Tacrolimus	Immunomodulator (organ transplant, autoimmune conditions)	Narrow therapeutic index, neurotoxicity	CYP3A5*1 allele (expressers) more prevalent in African ancestry; associated with increased tacrolimus dose requirements compared to CYP3A5*3 homozygotes common in Europeans/Asians.	More neurologic adverse effects (e.g. tremor, headache) reported in females.	PMID: 32657689 PMID: 25801146 PMID: 39041443 PMID: 37645617
Tamoxifen	ER-positive breast cancer	Endometrial cancer, thromboembolism	CYP2D6*10 genotype (reduced activity) prevalent in certain Asian groups and linked to poorer outcomes. Other relevant genes include CYP2C9, ABCB1, SLCO1B1.	Higher risk of thromboembolism in females.	PMID: 33515076 PMID: 30572423
Trastuzumab (Herceptin)	HER2-positive breast cancer	Cardiotoxicity	Women of African ancestry have up to a twofold higher risk of cardiotoxicity from trastuzumab compared to white women, potentially due to genetic and non-genetic factors	No known sex-associated differences reported.	PMID: 35420375
Valproic Acid (VPA)	Epilepsy	Teratogenicity, reproductive and sexual dysfunctions, hepatotoxicity, neurotoxicity	Polymorphisms in CYP2C9, CYP2C19, UGT1A6, and UGT2B7 influence VPA metabolism. UGT1A haplotype variation in Japanese and Asian populations contributes to differential VPA responses.	Higher teratogenic risk in women.	PMID: 38790997 PMID: 28726062 PMID: 23167925 PMID: 28878340 PMID: 16314888
Warfarin	Anticoagulation	Bleeding risk	African ancestry associated with significantly higher bleeding risk during warfarin therapy than European ancestry.	Lower incidence of major bleeding in females compared to males.	PMID: 28806200 PMID: 30357299 PMID: 32222786

Figure 1



Stem cells capture factors of human diversity and enable inclusive preclinical drug development studies. Left: Various layers of patient diversity that are retained in human patient-derived stem cells. Center: Various approaches, standalone or combined aid in assaying patient diversity, including standardizing assay protocols and readouts, automating parallelized cultures, deploying gene editing techniques to model specific genetic variants across different genetic ancestries or using pooled population and chimeroid organoid models to assay multiple donors simultaneously. Right: The outcomes of inclusive pre-clinical studies include:
Enhanced Drug Efficacy and Safety to ensure that drugs are effective and safe for a wide range of genetic backgrounds, minimizing adverse reactions across diverse populations.
Advanced Precision Medicine to facilitate the development of personalized therapies tailored to specific genetic and ethnic groups, optimizing treatment outcomes for each population.
Deeper Insights into Disease Mechanisms to provide a more comprehensive understanding of disease causes and progression across different genetic and ethnic backgrounds, uncovering population-specific risk factors.
Reduction in Health Disparities to help bridge gaps in health outcomes by making treatments more inclusive and effective for all populations, promoting equitable healthcare.
Higher Clinical Trial Success Rates to improve the predictive accuracy of preclinical models, leading to greater success in clinical trials by accounting for diverse responses early in the research process. This artwork was partially created using BioRender.com.

human pluripotent stem cells (hPSCs) or adult stem cells (AdSCs), they can be generated from both healthy and diseased donors, enabling detailed analysis of genetic and phenotypic diversity [32]. Unlike primary human cells, which often suffer from limited lifespan and functional decay, stem cell-derived organoids can be cultured long-term, genetically manipulated, and differentiated into disease-relevant cell types. This flexibility makes them well-suited for modeling individual and population-level genetic variations. Nevertheless, many current stem cell and organoid biobanks are skewed toward lines from individuals of Northern European ancestry, mirroring biases in broader genetic research [4].

Organoids have already demonstrated value in exploring ancestry-related pharmacogenomic variation. For example, breast cancer organoids derived from African ancestry patients were used to identify kinases essential for tumor viability through CRISPR-Cas9 kinome screening [33]. This approach uncovered vulnerabilities unique to tumors from West African individuals. Similarly, prostate cancer organoids from African American patients recapitulated genetic alterations associated with aggressive disease — including into the MYC, PTEN, TP53, and AR pathways disruptions - offering valuable insights into molecular contributors too outcome disparities [34].

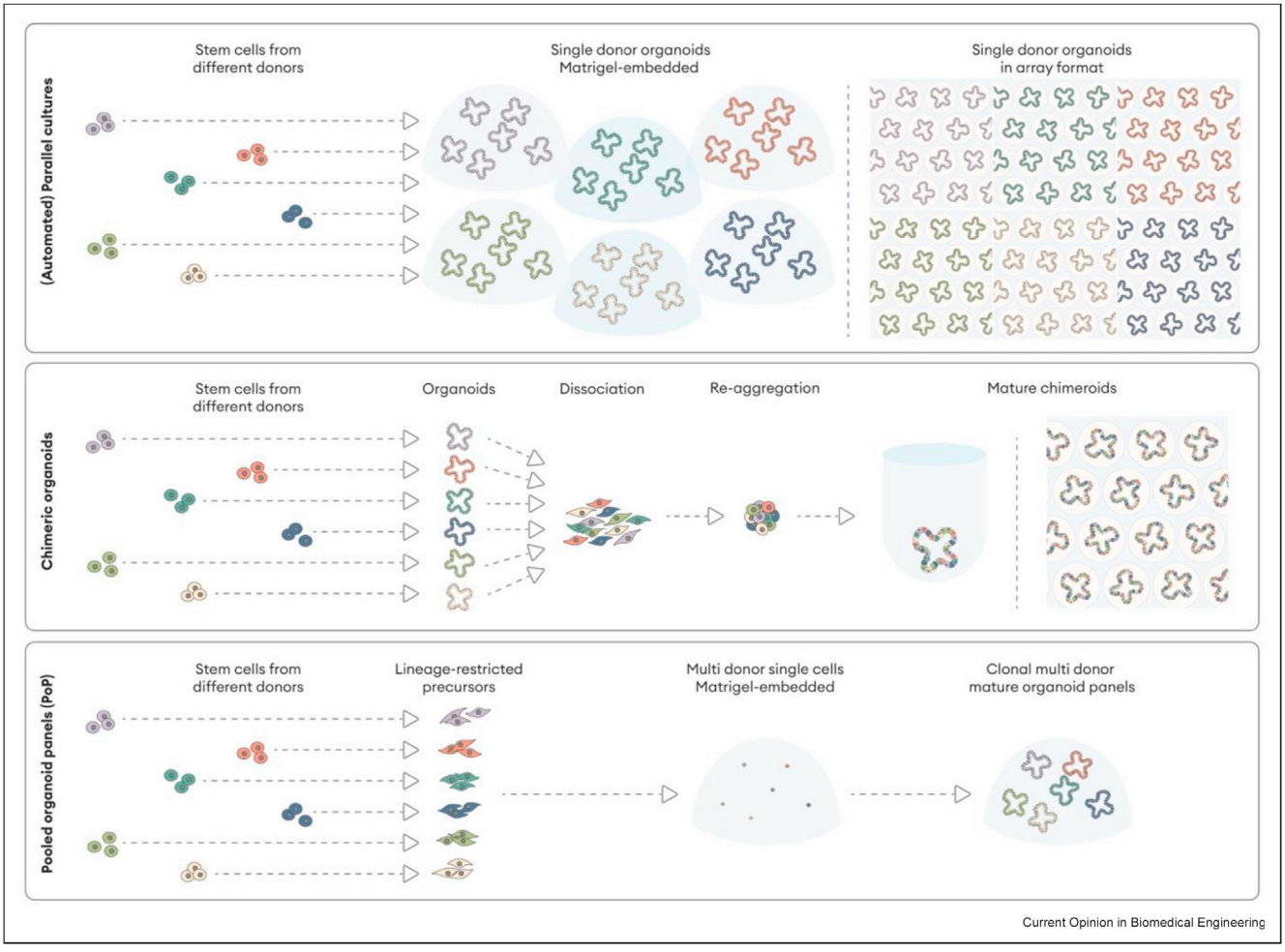
Beyond ancestry, organoids also enable modeling sex-based biological differences. In a study by Kelava et al., hPSC-derived brain organoids were used to examine sex differences in neurodevelopment [35]. They found that androgens, such as dihydrotestosterone (DHT), enhance excitatory neurogenesis in male organoids, resulting in increased excitatory neuron production. This observation parallels known sex differences in brain structure and may help explain male-biased

susceptibility to neurodevelopmental disorders like autism and schizophrenia.

Despite these strengths, modeling sex differences in hPSC-derived organoids presents challenges related to X chromosome inactivation (XCI) [36]. Female hPSCs often display unstable XCI, leading to variable expression of X-linked genes and complicating efforts to model dosage-sensitive traits. To overcome this, researchers should select lines with stable XCI and validated XIST expression. Monitoring XCI status throughout differentiation—e.g. through allele-specific expression analysis—can further ensure model fidelity.

Alternatively, adult stem cell organoids, which retain stable XCI, offer a robust platform for modeling sex-specific biology in a variety of tissues, including intestine, stomach, liver, pancreas, lung, kidney, and bladder [37–42]. For instance, adult stem cell colonoids have been used to investigate sex differences in colorectal cancer (CRC), a disease with higher metastasis and mortality rates in men [43]. In murine colonoid models, the Y-linked gene *KDM5D* was upregulated in males and associated with enhanced invasiveness, reduced cell adhesion, and repression of MHC class I antigen presentation – promoting immune evasion. Follow-up studies in human CRC lines confirmed that higher

Figure 2



Strategies for Modeling Population Diversity with Organoids.
The figure illustrates three main approaches to create organoid models for studying population diversity.
Top: Individual organoid lines cultured in parallel Matrigel or on micro-engineered hydrogel substrates, referred to as "organoid arrays."
Center and Bottom: Pooled systems ("village-in-a-dish"), including Chimeric organoids (Chimeroids) and Population Organoid Panels (PoP) [54,68].
• **Chimeroids**: Each stem-cell line is cultured independently to form early-stage organoids, which are then disaggregated, reassembled, and cultured into mature organoids. RNA sequencing and other single-cell methods can then identify cell types and track each line's contributions, enabling analyses of how genetic background impacts responses to compounds.
• **Population Organoid Panel (PoP)**: Organoids derived from mixed clonal progenitors of different donors in embedded Matrigel cultures. This approach creates mosaic organoids where over 90 % of each organoid originates from a unique donor. This approach can be verified by genomic PCR with donor-specific primers. The phenotypic responses of the PoP can be assessed using live and immunostaining techniques to visualize cellular responses at the individual-organoid level.

KDM5D expression correlated with worse survival in male patients.

Organoid systems can also be used to reflect dynamic hormonal environments relevant to sex-specific biology. For example, endometrial organoids have been used to study hormone-responsive tissue dynamics in reproductive health [44]. Further developments could include mimicking menstrual cycle through timed administration of estrogen and progesterone, or using vascularized organoids to enable continues hormonal exchange. These systems may dramatically improve the predictive accuracy of organoids in modeling sex-specific drug responses and reproductive health research.

The systematic inclusion of organoids representing different sexes and a wide range of ancestries in preclinical research represents a critical next step toward equitable, effective precision medicine. As organoid technology continues to evolve, it holds immense potential to close longstanding gaps in pharmacogenomic research and transform therapeutic development for diverse populations.

Capturing diversity: single vs. pooled approaches in organoid research

The need for *in vitro* models that accurately reflect human population diversity is underscored by insights gained from large-scale genetic databases, such as the 1000 Genomes Project and the Genome Aggregation Database (gnomAD). These resources show that capturing genetic diversity, including rare and population-specific variants, requires a varying number of genomes depending on the genetic variability of the group in question [45]. In organoid research, creating a population-representative panel may need 20–30 organoid lines for genetically homogenous groups, whereas populations with higher variability, such as those of African or Latin American descent, may need 50–100 lines to capture rare variants and prevalent alleles [46–49].

Researchers can explore population diversity in organoids through the use of individual organoid lines or pooled systems, also known as "village-in-a-dish" (Figure 2). Single organoid lines allow functional studies of specific genetic variants, shedding light on their roles in health and disease across diverse populations [50]. However, these studies can be limited by sample sizes and technical variability across donor lines and differentiation rounds. Recent advances in micro-engineered hydrogel substrates for organoid culture help reduce this variability by providing stable environments that promote uniform stem cell aggregation to create "organoid arrays", enhancing reproducibility in phenotypic assays [51]. Yet, scaling up individual organoid lines remains labor-intensive, encouraging the use of automation, such as robotic systems, to manage these lines effectively.

In contrast, pooled systems allow for the capture of population diversity at scale by integrating cells from multiple individuals into a single culture. These pooled cells can undergo desired perturbations or phenotyping, followed by genetic characterization to identify individuals based on their phenotypes of interest. This approach has shown promise in hPSC strategies, their 2D derivatives, extending to organoids as well [50,52,53] [68]. A recent study exemplified this concept by creating a multidonor brain organoid model, referred to as "Chimeroids," generated from cells of multiple donors aggregated into a single organoid [54]. This innovative system enables cells from diverse genetic backgrounds to develop together, resulting in a highly reproducible organoid that maintains balanced representation of cell types across donors. The Chimeroid model, highlighted the importance of genetic diversity in neurodevelopment and demonstrated that interindividual variability significantly influences responses to neurotoxic agents, such as ethanol and valproic acid (VPA).

These models allow for comprehensive studies of how genetic diversity influences organoid behavior and responses.

In summary, the choice between single and pooled approaches depends on the specific research question and the need for representation of genetic diversity. Both methods present unique advantages and limitations, making them complementary in the pursuit of more inclusive and representative biomedical research.

Challenges and opportunities in drug discovery and development

The evolving legislative landscape, including DEPICT, FDORA, and the FDA Modernization Act 2.0, has created a strong foundation for advancing diversity in drug development [55–57]. DEPICT and FDORA introduce mandates for diversity action plans in clinical trials, requiring sponsors to include underrepresented populations and to establish clear diversity targets [55,56]. Concurrently, the FDA Modernization Act 2.0 reduces the reliance on animal testing, encouraging innovative human-based models such as stem cell-derived organoids [57]. Although global clinical trials remain costly and time-intensive, stem cells and organoids can be readily generated from ancestrally and geographically diverse, sex-balanced donor samples. This presents a pivotal opportunity to embed equity and inclusion into the earliest stages of drug development, addressing disparities in drug efficacy and safety across populations [58]. Incorporating organoid systems that reflect diverse genetic backgrounds, enhances the

relevance and translatability of preclinical assessments, ultimately leading to safer and more effective therapies for a broader patient population.

Leading academic institutions and pharmaceutical companies are increasingly validating stem cell-derived organoid models for specific applications, such as assessing drug-induced gastrointestinal toxicity and liver injury [59–61]. These initiatives help to build a stronger foundation for the further qualification of organoid models through regulatory mechanisms like the FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) pathway, thereby boosting confidence in these systems among pharmaceutical companies and regulatory bodies.

However, many current studies rely on a narrow set of donor lines that lack comprehensive demographic diversity. Expanding these models to include a wider range of donor samples would enable deeper insights into population-specific differences in drug metabolism, safety and efficacy. Importantly, this expansion could facilitate the identification of novel pharmacogenomic variants and support the study of rare variants more prevalent in certain populations – potentially reducing the number of samples required to reach statistical significance.

Increasing diversity in drug development also has significant socio-economic implications, particularly for historically understudied populations. In both low- and high-income countries, more equitable drug development could reduce healthcare costs by minimizing ADRs, improving treatment outcomes, and avoiding prolonged hospital stays. Additionally, localizing organoid research empowers regional decision-making by aligning drug development with local disease burdens and population-specific needs. For instance, regionally adapted pharmacogenetic (PGx) screening in South Africa that considers continent's unique genetic diversity and healthcare challenges could reduce ADRs by up to 30 % [12].

Despite these opportunities, limited access to diverse donor samples remains a major challenge in both academia and industry [50,58]. In response, several countries have established HLA-matched iPSC biobanks to provide immunologically relevant and genetically defined cellular resources. These biobanks curate iPSC lines derived from donors with homozygous HLA haplotypes common in their respective populations, enabling the generation of cell types and organoids with reduced immunogenicity and broad applicability. Japan's CiRA iPSC stock project [62], for instance, was designed to ultimately cover over 80 % of the Japanese population using a few dozen HLA-homozygous lines. Similar efforts are underway in the UK, USA, and South Korea [63]. While originally established for regenerative therapies, these haplobanks are increasingly recognized as valuable resources for disease modeling and drug screening – especially in contexts where HLA-relevant or population-specific immune responses are a concern [64]. However, these initiatives remain insufficient to meet the global demand. Most haplobanks are concentrated in high-income countries and reflect limited genetic diversity, restricting their utility for global populations.

To address this gap, governments and non-profit organizations must play a pivotal role in developing locally representative tissue and organoid biobanks that are globally accessible. A promising strategy involves establishing national biobanking programs – potentially integrated with organ donation systems and iPSC infrastructure – to support local clinical trials and translational research. Finland's FinnGen project [65] exemplifies how public-private partnerships can effectively integrate genetic data and health records to advance precision medicine. Encouragingly, researchers in resource-limited regions such as Africa are beginning to generate iPSCs from continent's vast genetic diversity [66,67]. These initiatives demonstrate that historically underrepresented regions can play a leading role in expanding access to genetically diverse organoid models. Through North-South collaborations that prioritize regional capacity building, the establishment of regional centers of excellence, and equitable global funding mechanisms, these efforts can contribute significantly to inclusive drug development.

To ensure global equity, adapted biobanking models must also address ethical oversight and cultural sensitivity in donor engagement and consent. Cultural norms around sample export and the use of human biological materials vary significantly across regions, influencing the terms of material sharing and use. Respecting these differences through transparent, community-informed consent processes is essential. Moreover, large sample sizes are often required to achieve the statistical power necessary to detect population-level biological trends. Overcoming these challenges will require advances in high-throughput organoid production, robust phenotypic screening platforms, and standardized protocols that minimize experimental variability. These efforts should be complemented by detailed clinical phenotyping and computational modeling to map genotype–phenotype relationships across health and disease.

Finally, bridging the gap between *in vitro* findings and clinical applications will demand sustained investment and cross-sector collaboration among academic institutions, medical centers, industry, policymakers, and funders. To truly enable diversity-driven innovation in drug discovery, the global research ecosystem must financially prioritize and incentivize inclusive, population-relevant research.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGpt in order to check for grammar, spelling and potential improvements in the clarity of the manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sylke Hoehnel-Ka reports a relationship with Doppl SA and SUN bioscience SA that includes: board membership, employment, and equity or stocks. The Ecole Polytechnique Fédérale de Lausanne has filed for patent protection on the technology described herein (WO2018/050862 and WO2018/050862), and S.H.K. is named as inventors on those patents; S.H.K. is shareholder in Doppl SA and SUN bioscience SA, who are commercializing those patents. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Francesco Piraino reports a relationship with Doppl SA that includes: employment.

All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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- • of special interest
- •• of outstanding interest

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