sites in different cancer types. If the target of CTCF site alterations is destruction of insulated neighborhoods, then only boundary CTCF sites should be enriched for mutations. Across a large pan-cancer cohort, the authors observed a factor of >2 enrichment for boundary CTCF site mutations. This enrichment was particularly strong in liver and esophageal carcinomas, where boundary CTCF site mutations were also significantly more likely to be found near known oncogenes. Whether this enrichment is driven primarily by activation of proto-oncogenes is not clear, and further analyses are needed to uncover the specific gene targets driving CTCF site alterations within different tumor types. Such studies may also be useful for clinical genotyping, where identification of activated oncogenes is a key step in applying the optimal targeted therapy.

Genetic events that disrupt insulated neighborhoods may be just one of many ways that cells alter their 3D chromatin structure to dysregulate gene expression. Recently, Flavahan *et al.* reported that disruption of TADs by DNA methylation of boundary CTCF sites allows a distant active enhancer to interact with and drive a key oncogene in brain tumors (*10*). Together with the findings of Hnisz *et al.*, these pioneering studies highlight the diversity of mechanisms by which chromatin structure may be targeted and suggest that modulating 3D chromatin structure may be widespread in cancer.

By showing that disruption of insulated neighborhoods leads to activation of proto-oncogenes, Hnisz *et al.* describe a previously unrecognized mechanism by which cancers may escape transcriptional regulation. This study adds to an expanding understanding of the deep impact that alterations outside of protein-coding regions can have in driving the expression of cancer genes (*11*–*13*). Future research aimed at deciphering such noncoding alterations in cancer will need to account for perturbations to the 3D architecture of the genome, while also being alert to indications of novel methods of transcriptional dysregulation. ■

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RESEARCH ETHICS

Ethics review for international data-intensive research

Ad hoc approaches mix and match existing components

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POLICY

Historically, research ethics committees (RECs) have been guided by ethical principles regarding human experimentation intended to protect participants from physical harms and to provide assurance as to their interests and welfare. But research that analyzes large aggregate data sets, possibly including detailed clinical and genomic information of individuals, may require different assessment. At the same time, growth in international data-sharing collaborations adds stress to a system already under fire for subjecting multisite research to replicate ethics reviews, which can inhibit research without improving the quality of human subjects' protections (*1*, *2*). "Top-down" national regulatory approaches exist for ethics review across multiple sites in domestic research projects [e.g., United States (*3*, *4*), Canada (*5*), United Kingdom, (*6*), Australia (*7*)], but their applicability for data-intensive international research has not been considered. Stakeholders around the world have thus been developing "bottom-up" solutions. We scrutinize five such efforts involving multiple countries around the world, including resource-poor settings (table S1), to identify models that could inform a framework for mutual recognition of international ethics review (i.e., the acceptance by RECs of the outcome of each other's review).

Data-intensive projects often raise ethical concerns for which RECs have little guidance. Data can be collected from consenting participants at one site but stored, analyzed, or linked with data sets elsewhere. Data are typically stored for long periods and can be reused and (re)linked. Particularly problematic is that perceived and legislated ownership of data and the responsibility to authorize data sharing varies across jurisdictions. Investigators and RECs must consider the security of data management, how the privacy of participants will be assured, and the overall governance (e.g., use and access) of a data set.

We exclude from our analysis clinical trials work, which is led by the International Council (formerly Conference) on Harmonisation (*8*), although we note increasing convergence of clinical trials with large, heterogeneous data sets (*9*).

MODELS AND PRINCIPLES. Our analysis revealed three general ethics review models—reciprocity, delegation, and federation—that clarify and add to what currently exists in some jurisdictions and integrate existing ethics review approaches in innovative ways (see table). Each project used several mechanisms to achieve greater cross-jurisdictional mutual recognition of ethics review (table S2). Prior and ongoing engagement with RECs, institutions, or governmental bodies to achieve REC alignment (e.g., a memorandum of understanding) can be effective. A well-resourced process for developing tools (e.g., customized agreements or face-to-face meetings) for improved REC review is critical, as is (if possible) an opportunity to pilot test them before full implementation.

Ethics review for data-intensive international research should be founded on at least two principles. First, projects imposing similar risks on research participants should be subjected to similar levels of scrutiny by all RECs. Second, if we assume that procedural and regulatory alignment is in place, once an ethics review opinion has been provided, each jurisdiction should not require further de novo review. This does not foreclose local accommodations for is-

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Three models for building ethics review mutual recognition for data-intensive international research

	ADVANTAGES	DISADVANTAGES	PROJECTS
RECIPROCITY An institution, funder, or regulator/government in one jurisdiction accepts the completed ethics review from another jurisdiction and vice versa through collaborative recognition of equivalent processes and/or standards	Helps build agreement on research participant protections while respecting local context Flexibility with review standards Potentially time-saving once a decision on equivalence is reached, if applied to a whole class of projects	Some REC system inefficiencies remain (e.g., inconsistent or incompatible opinions) Challenge in defining whose protections are "best" Time-consuming at the initial implementation stage	Human Heredity and Health in Africa (H3Africa): shared ethics consultation meetings to build trust and REC alignment International Cancer Genome Consortium (ICGC): development of ethics review policies Personalized Risk Stratification for Prevention and Early Detection of Breast Cancer (PERSPECTIVE): customized tools and agreements approved by each institution
DELEGATION Before review, an institution, funder, or regulator/government delegates ethics review responsibilities to one or several existing designated RECs through agreement	Reduces the potential for inconsistency Researchers can channel energy and resources into one or a few RECs Increased possibility for specific areas of ethics expertise in the designated REC(s)	Challenge in determining how a REC is chosen Challenge in determining how post-approval activities will be handled All-or-nothing outcome of review; no room for alternative reviews	ICGC: agreements signed between ministries of health
FEDERATION Institutions, funders, or regulators/governments create a central REC with representation from multiple jurisdictions	Reduces costs and duplication of efforts Reduces inconsistency in REC review Drives improved standards across sites by encouraging a "herd instinct"	Challenge in developing REC structure and process Challenge in balancing cultural representation, power differences, or local priorities Challenge in getting several jurisdictions to agree on policy and standards	Indiana University–Moi University (IU-Moi): proposed REC with members of each institution Maternal Infant Child & Youth Research Network (MICYRN): federated pediatric REC across Canada

sues pertinent to local context (e.g., data storage or recruitment methods).

RECs are likely to be more supportive of mutual recognition frameworks if acceptable safeguards are in place and there are guarantees that, in case of a personal data breach, participants can bring an action (i) individually in their own jurisdiction and (ii) collectively. RECs could have a role in working with other bodies, such as data access committees, data protection authorities, funding agencies, journals, and research employers to assure that storage and use of data are properly monitored and reported, which includes material data breaches and action taken. Although there will always be some inconsistency within and between RECs, there must also be core opinions and underlying rationales deemed acceptable by researchers, research participants, and society (*10*).

Any successful model of ethics review for data-intensive international research must sustain key functions: robust protection of research participants; the gatekeeping role of a REC during the research life cycle; integrity of the ethics review system and of each REC; and trust in the ethics review standards and processes to collect, store, share, and access data.

Although no one model will fully suit all data-intensive international research and multiple variations can be devised, we believe that the models identified here can improve on the status quo of replicate REC review. Until the emergence of a competent and legitimate system for reviewing and steering data-intensive international research, we advocate bottom-up, ad hoc solutions, ideally coupled with official recognition and support by governments and regulators, sponsors, funders, institutions, and data access committees. As models are tested and improved, more systemic solutions can be implemented.

Organizations have a key role to play. For instance, the Global Alliance for Genomics and Health has developed policies on accountability, consent, and privacy and is engaging stakeholders on the research ethics governance of data-intensive projects (*11*). This may assist RECs that need to check the consistency of secondary data uses with the original consent forms or verify the adequacy of data protection measures or consent processes.

In addition to moving toward common ethics review standards and procedural alignment, common conditions for exchanging data should be developed, which we believe would make RECs more inclined to mutual recognition of ethics review.

Given the global scale of the task and the bottom-up nature of this approach, at this stage, there needs to be international commitment to test these models and variations to determine whether they can achieve the desired alignment in ethics review of data-intensive research. Evidence suggests that the current system is not working well; evidence is now needed to show whether certain alternatives are better. This will necessitate defining metrics to evaluate the quality and efficiency of ethics review both in the current system and in the proposed models (*12*). Communication with and between RECs will be crucial. The era of collaborative data-intensive international research gives us an opportunity to reform the way in which ethics committees across the world work. ■

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SUPPLEMENTARY MATERIALS

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