LETTERS

edited by Jennifer Sills

Keeping Raw Data in Context

WE AGREE WITH THE PREMISE STATED IN "MAKING CLINICAL data widely available" (Special Section on Clinical Trials, J. Kaiser, 10 October 2008, p. 217): Sharing patient-level data from human studies would help investigators make more and better discoveries more quickly and with less duplication. However, this happy circumstance will occur only if investigators interpret the raw data properly within the context of the study that generated that data. This implies that any initiative to share raw clinical research data must also pay close attention to sharing clear and complete information about the design of the original studies. Relying on journal articles for study design information is problematic, for three reasons. First, journal articles often provide insufficient detail when describing key study design features such as randomization (*1*) and intervention details (*2*). Second, some data sets may come from studies with no publications [only 21% of oncology trials registered in ClinicalTrials.gov before 2004 and completed by September 2007 were published (*3*)]. Finally, investigators cannot reliably search journal articles for methodological concepts like "double blinding" or "interrupted time series," crucial concepts for proper interpretation of the data. A mishmash of nonstandardized databases of raw results and unevenly reported study designs is not a strong foundation for clinical research data sharing.

Data sharing. Shared data will only be useful if complete information about the original study design is also available.

We believe that the effective sharing of clinical research data requires the establishment of an interoperable federated database system that includes both study design and results data. A key component of this system is a logical model of clinical study characteristics in which all the data elements are standardized to controlled vocabularies and common ontologies to facilitate cross-study comparison and synthesis (*4*). As a first step toward this vision, the Human Studies Database Project is developing a standardized representation of study designs for all ongoing human studies at NIH-funded Clinical and Translational Science Award (CTSA) institutions, with the ultimate goal of using these standards to integrate local institutional databases of human studies for large-scale data sharing and reuse (*5*). This approach would also support legally mandated trial registration and results reporting (*6*), NIH-related data sharing initiatives (*7*, *8*), and requests for raw data by biomedical journals (*9*). To complement work on defining and standardizing study design descriptions, national and international policies are still urgently needed to ensure effective, ethical, and coordinated sharing of tightly coupled study design and raw patient-level data (*10*).

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The IRB Is Key

IN HIS RESPONSE TO A LETTER ON HIS PERspective "*Homo experimentalis* evolves" (*1*) (31 October 2008, p. 672), J. A. List replies that the economic research he conducted did not require informed consent by the unwitting participants because the study yielded interesting results and did no harm. The response concludes, "Those cases in which there are minimal benefits of informed consent but large costs are prime candidates for relaxation of informed consent."

There are certainly grounds for dispensing with informed consent in social sciences research, and Institutional Review Boards (IRBs) have guidelines for doing so. However, there are no general rules that cover every instance, and the investigator does not have the authority to make the decision about when the guidelines apply. Instead, exemptions are granted by IRBs only on a case-by-case basis. In this case, the appropriate question is, did List submit his research protocol to his supervising IRB and request an exemption? The decision to dispense with informed consent is not the author's.

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Response

AS MY LETTER SUGGESTS, INSTITUTIONAL REVIEW Boards (IRBs) are a necessary condition and serve an invaluable role; I wrote, "Local

Research Ethics Committees and Institutional Review Boards in the United States serve an important role in monitoring such activities." All of my research has IRB approval, and I suspect from W. R. Lovallo's concerns that he and I agree on all aspects of subject approval. In my own research, I have been even more stringent than IRB requirements—I do not deceive subjects and always ensure that they are better off due to my experiment. These conditions are certainly not a constraint in all, or even many, IRBs that I am aware of.

On another note, some researchers do not have Local Research Ethics Committees and Institutional Review Boards. Outside the United States, researchers in the social sciences must rely largely on their own moral principles. I view my letter as also speaking to these scholars and letting them know that strict standards need to be followed.

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Implications of Ancient Ice

IN THEIR BREVIA "ANCIENT PERMAFROST AND a future, warmer Arctic" (19 September 2008, p. 1648), D. G. Froese *et al.* reported the discovery of an ice wedge more than 740,000 years old within the discontinuous permafrost zone of central Yukon Territory, Canada. Permafrost in this area is warm (with an average temperature greater than –2°C) and strongly controlled by local site conditions. It is generally sparse or absent on south-facing slopes and in areas lacking insulating vegetation cover.

Permafrost is very sensitive to climate change: If the average annual air temperature changes by several degrees, then the temperature of soil and permafrost soon will change by the same amount (*1*–*3*). Therefore, a 2°C warming there would lead to permafrost degradation in the Yukon Territory. By assuming that temperatures during at least two previous interglacials were substantially warmer than those today, Froese *et al*. conclude that the persistence of that ice wedge implies that permafrost can be more stable than previously thought.

Their conclusion may not be valid, for two reasons. First, Froese *et al*. provide no evidence that average annual temperatures in the Yukon Territory were higher during previous interglacials than they are today. Second, there is no physically substantiated explanation of how permafrost could be stable across such climate warming. Permafrost stability during warmer interglacials would seem to require that the permafrost was covered with a massive layer of organic insulator, such as moss or peat, in order to prevent summer heating of soils. Such a condition seems to be contradicted by the facts that such a cover does not exist there today and that there is no evidence that widespread fires might have burned any such cover had it once existed. Consequently, a simpler explanation of why the ice wedge did not melt during the past 740,000 years is that this territory was never substantially warmer then it is today. **SERGEY ZIMOV**

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Response

WE THANK S. ZIMOV FOR HIS INTEREST IN our Brevia. Zimov does not agree that the persistence of ice wedges in Yukon Territory for more than 700,000 years reflects thermal resilience of permafrost more than a few meters below the surface. He instead interprets our finding as evidence that tempera-

CORRECTIONS AND CLARIFICATIONS

Letters: "Unsung hero Robert C. Gallo" by G. Abbadessa *et al*. (9 January, p. 206). Author Riccardo Dalla-Favera's name was spelled incorrectly. The misspelling has been corrected online.

Random Samples: "Getting there" (2 January, p. 19). The credit should have been Andrew Nelson/Joint Research Center of the European Commission.

News Focus: "Shortfalls in electron production dim hopes for MEG solar cells" by R. F. Service (19 December 2008, p. 1784) contained several inaccuracies. A 2004 paper by Victor Klimov and colleagues reported multiple exciton generation (MEG) in lead selenide nanocrystals, not lead sulfide as reported. The maximum efficiency at the time was 220% for a photon energy equal to 3.8 times the nanocrystals' band gap. This was later increased to 268% at 4.3 times the band gap. (The 700% efficiency reported was produced using photons with 7.8 times the nanocrystal band gap.) More recent results for stirred solutions saw the efficiency decline not to 40% as stated, but to 150% for photons 4.3 times the bandgap, only slightly higher than the 123% seen by Moungi Bawendi's group at MIT for the same ratio of the photon energy to energy gap. The difference in the MEG effect between different nanocrystal samples in the case of stirred solutions was 30%, not 300% as reported.

The sentence "Synthetic differences between samples may have left some with surfaces that enhance the effect" should have stated simply that the surface variation between samples likely accounts for some of the variation of the effect. The Los Alamos team stirred the samples to keep the nanoparticles from absorbing more than one photon from sequential laser pulses, not "more than one photon at a time." Klimov does not consider the new results "bad news," but agrees that the effect is too small to make a practical difference for current solar cells. The MEG effort at the National Renewable Energy Laboratory is led by Arthur Nozik; the group treated solar cells made with nanocrystal films with ethanedithiol, not hydrazine.

An E-Letter with further clarifications has been published online at www.sciencemag.org/cgi/eletters/322/5909/1784a.

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Human-Specific Gain of Function in a Developmental Enhancer"

Laurent Duret and Nicolas Galtier

Prabhakar *et al*. (Reports, 5 September 2008, p. 1346) argued that the conserved noncoding sequence *HACNS1* has undergone positive selection and contributed to human adaptation. However, the pattern of substitution in *HACNS1* is more consistent with the neutral process of biased gene conversion (BGC). The reported human-specific gain of function is likely due to the accumulation of deleterious mutations driven by BGC, not positive selection.

Full text at www.sciencemag.org/cgi/content/full/323/5915/714c

RESPONSE TO COMMENT ON "Human-Specific Gain of Function in a Developmental Enhancer"

Shyam Prabhakar, Axel Visel, Jennifer A. Akiyama, Malak Shoukry, Keith D. Lewis, Amy Holt, Ingrid Plajzer-Frick, Harris Morrison, David R. FitzPatrick, Veena Afzal, Len A. Pennacchio, Edward M. Rubin, James P. Noonan

Duret and Galtier argue that human-specific sequence divergence and gain of function in the *HACNS1* enhancer result from deleterious biased gene conversion (BGC) with no contribution from positive selection. We reinforce our previous conclusion by analyzing hypothesized BGC events genomewide and assessing the effect of recombination rates on human-accelerated conserved noncoding sequence ascertainment. We also provide evidence that AT → GC substitution bias can coexist with positive selection.

Full text at www.sciencemag.org/cgi/content/full/323/5915/714d