

SCIENCE'S COMPASS

maths and Theoretical Computer Science, E. Winfree, D. K. Gifford, Eds. [American Mathematical Society, Providence, RI, 2000], p. 91] of large numbers of both sequencing primers and iDNA sequences that satisfy the constraints on these elements.

6. The DNA bases were ordered alphabetically (A, C, T). DNA codons were then constructed by means of a ternary code, beginning with "AAA" (encoding the letter "A"). The bases C, and then T, were inserted progressively into the third, second, and first positions, yielding a series of 27 codons encoding the English letters in alphabetical order, plus a space (8).
7. C. Dickens, *A Tale of Two Cities* [Oxford Univ. Press, London, New York, 1953 (originally published in 1859)].
8. Supplementary material is available at <http://www.sciencemag.org/cgi/content/full/293/5536/1763/DC1>
9. The combined operations of PCR followed by sequence analysis are analogous to the retrieval of information from an addressable storage device such as the random access memory in a computer. The ability to use these combined operations to retrieve data permits construction of DNA representations of classical computer data structures such as arrays, linked lists, and trees. The model depicted in the figure is somewhat analogous to an array data structure. The PPK contains the addresses of the data elements (the iDNA segments), which can be calculated (sequenced) and then used for selective retrieval of the stored data. In an alternative serial model, analogous to a linked list, a series of iDNAs could be designed, each containing both a data element and the sequencing primer for retrieving the data element from the succeeding iDNA. Such a serial model would obviate the need for a separate PPK, but information retrieval would require considerably more experimental manipulations (and prior specific knowledge) than in the parallel model explored here.
10. D. Gerhold, T. Rushmore, C. T. Caskey, *Trends Biochem.*

Sci. 24, 168 (1999).

11. There is a theoretical maximum of 4^{20} , but this number would be reduced by the requirement that primer sequences be designed to avoid mispriming at inappropriate sites.
12. A conservative upper limit on the size of the information segment is ~600 bases, set by the present limits on DNA sequence obtainable from a single sequencing primer. If four-base codons chosen from our three-base alphabet (A, C, T) were used (to permit encoding of all common English alphanumeric characters plus a space), each iDNA could store about 150 characters. Storage of *A Tale of Two Cities*, containing 742,901 alphanumeric characters plus spaces, would require ~5000 iDNAs. Current technology would permit single-pass sequence analysis of a single PPK containing up to 100 unique sequencing primers, implying that information could be stored in ~100 different iDNAs per microwell. Since 50 microwells would thus be required to store Dickens' novel in DNA form, a 10,000-well microchip could store ~200 texts.
13. Supported by Defense Advanced Research Projects Agency/National Science Foundation grant CCR-9724012.

The Challenge of Defining Disease

THE PHILOSOPHICAL DEFINITION OF DISEASE based on impairment or limitation of normal function that Boorse (1) proposed is rejected as being clinically impractical by L. K. F. Temple and co-authors in their Essay "Defining disease in the genomics era"

(*Science's Compass*, 3 Aug., p. 807). However, the definition they offer seems too broad and also fraught with its own set of difficulties.

Temple *et al.* write that "disease is a state that places individuals at increased risk of adverse consequences." According

"...activities such as mountain climbing or bungee jumping could be construed as disease states."

to this definition, activities such as mountain climbing or bungee jumping could be construed as disease states. If we could provide appropriate modifiers for the words "state" and "adverse consequences," then we would be better poised to begin a more precise definition of disease in the genomics era.

NHLBI Mammalian Genotyping Service



The Mammalian Genotyping Service is funded by the National Heart, Lung, and Blood Institute to assist in linkage mapping of genes which cause or influence disease and other research purposes. Genotyping is carried out using whole genome polymorphism scans at Marshfield, Wisconsin under the direction of Dr. James Weber. Capacity of the Service is currently about 7,000,000 genotypes (DNA samples times polymorphic markers) per year and growing. Although the Service was initially established for genetic projects dealing with heart, lung, and blood diseases, the Mammalian Genotyping Service will now consider all meritorious applications. Genome scans for humans, mice, rats, dogs and zebrafish are available.

To ensure the most promising projects are undertaken, investigators must submit a brief application which will be evaluated by a scientific advisory panel. At this time, only projects with at least 10,000 genotypes will be considered. DNA samples must be in hand at the time of application. Most genotyping within the Service is currently done with multiallelic STRPs (microsatellites). However, genotyping with human diallelic polymorphisms has been initiated and will likely expand. **There are no genotyping fees for approved projects.** The Service is funded through September, 2006. Application deadlines are every six months.

Upcoming Deadlines:

March 31

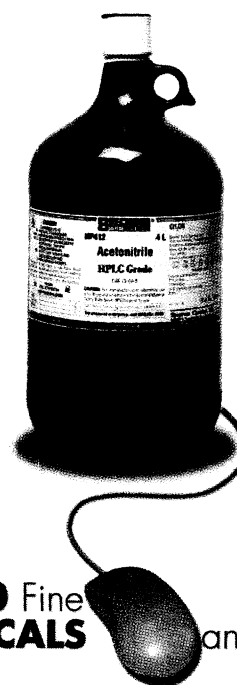
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Taking the essential elements of Boorse (1) and Temple *et al.*, I suggest the following definition: Disease is a genotypic or phenotypic state, often influenced by environmental factors, that places individuals at risk for internally derived adverse consequences.

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References and Notes

1. C. Boorse, in *Biomedical Ethics Reviews: What Is disease?*, M. Humber, R. F. Almeder, Eds. (Humana, Totowa, NJ, 1997), pp. 7–8.

Response

BUNGEE JUMPING AND MOUNTAIN CLIMBING are activities rather than states and, therefore, would not necessarily be considered diseases. However, no definition of disease will work in all contexts. Risk-taking behaviors may be better dealt with by Clouser *et al.*'s definition of a malady as "a condition other than rational beliefs or desires, such that [individuals] are incurring, or at a significantly increased risk of incurring, a harm or evil (death, disability, loss of freedom, or loss of pleasure) in the absence of direct sustaining cause" (1). One might argue about the ratio-

nality of either climbing up or jumping off heights. Furthermore, given the potential genetic explanations for behavioral disorders such as risk-taking behavior (2), with time, bungee jumping and mountain climbing might be viewed by some as disease manifestations.

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References and Notes

1. K. D. Clouser, C. M. Culver, B. Gert, in *Biomedical Ethics Reviews: What Is disease?*, J. M. Humber, R. F. Almeder, Eds. (Humana, Totowa, NJ, 1997), pp. 173–218.
2. D. E. Comings, K. Blum, *Prog. Brain Res.* **126**, 325 (2000).

CORRECTIONS AND CLARIFICATIONS

PERSPECTIVES: "Dicing up RNAs" by V. Ambros (3 Aug., p. 811). In the last paragraph on p. 811, a reference number is erroneously stated. Reference number (1) on line 4 should have been written as reference number (10), citing a paper by E. Bernstein *et al.*, *Nature* **409**, 363 (2001).

CORRECTIONS, REPORTS: In the 27 July issue (p. 607), in the correction for the report "Quantum mechanical actuation of microelectromechanical systems by the Casimir force" by H. B. Chan *et*

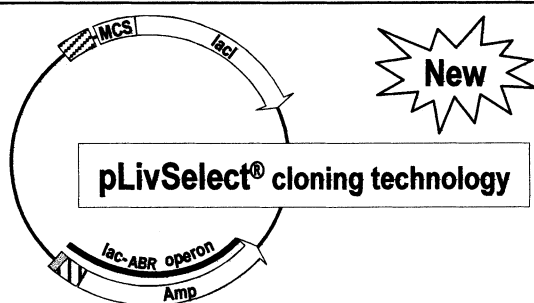
al. (9 Mar., p. 1941), a delta symbol in the expression $F_2(\Delta z + z_1)$ printed as a capital "D."

REPORTS: "Calibration of the lutetium-hafnium clock" by E. Scherer, C. Munker, K. Mezger (27 Jul., p. 683). In note 47, an "f" was inadvertently inserted in front of "cgi" in the URL for the supplemental Web material. The correct URL is www.sciencemag.org/cgi/content/full/293/5530/683/DC1

NEWS OF THE WEEK: "Interest blooms in growing jellyfish boom" by D. Malakoff (6 Jul., p. 29). *Mnemiopsis leidyi* was incorrectly referred to as a jellyfish (phylum Cnidaria); it is a comb jelly (phylum Ctenophora).

REVIEW: "The early evolution of the inner solar system: A meteoritic perspective" by C. M. O'D. Alexander, A. P. Boss, R. W. Carlson (6 Jul., p. 64). The y-axis label for Fig. 2C was incorrect. The label should have read "(Abundance - xCI)/CI/(1 - x)."

PERSPECTIVES: "How to make a superior cell" by G. Stephanopoulos, J. Kelleher (15 Jun., p. 2024). In paragraph 1, members of the genus *Streptomyces* were misidentified as "fungus" rather than as bacteria. The mistake does not affect the central points of the article.



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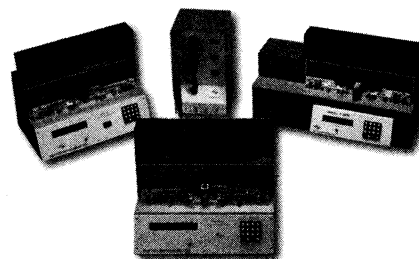
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