



Environmental Health Issues

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Abstract

Biomarkers are potentially powerful tools for use in research and regulation. Their derivation from biologic specimens collected from human subjects does, however, present many ethical implications. Ethical issues are relevant in almost each facet of human biomarker research studies: design, identification and recruitment of subjects, handling and use of the data, and interpretation and communication of results. Researchers also face a number of dilemmas when considering the use of human biologic specimens and new biomarkers. The mere fact that such markers are the result of measurements in human specimens gives the appearance of being more accurate than traditional sources of information such as questionnaires or environmental monitoring; yet, this may not always be the case. The meaning of the results of biomarker studies may be unclear because the purpose of the study is usually for research rather than clinical purposes. There generally are no established normal ranges for biomarkers and the interpretation of findings are often difficult. Researchers may not communicate these results to subjects or consider followup action because the task may be too difficult or undefined, or the reaction of the subject cannot be anticipated. A wide range of practices in this regard exists among researchers. Many questions remain unanswered about the use of biologic specimens. These include questions of ownership and access to specimens. Related to this is the question of whether specimens collected for one research purpose can be used for an entirely different research purpose. This is still an open question. Researchers and regulators may not be aware of the potential for biomarker information to affect the lives of subjects and their families without sufficient protection of personally identifiable data and regulation of its use. It is incumbent on researchers to consider these human subject questions whenever they are using human specimens or biomarkers. --

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Ethical Considerations, Confidentiality Issues, Rights of Human Subjects, and Uses of Monitoring Data in Research and Regulation

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Abstract

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Key words: ethics, confidentiality, privacy, informed consent, human subjects, biomarkers, study design, biologic specimens, specimen banking

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Introduction

The use of human biologic specimens is integral to current advances in molecular epidemiologic research and biotechnologic development. In the environmental health field, biomarkers collected from human specimens are now being used to indicate exposure, disease, or susceptibility (1). Studies involving biologic markers have the potential to involve a broad range of ethical, legal, and social issues. These studies are characterized by the actual collection of biologic specimens from individual subjects. Biomarker assays on human specimens have the potential to be powerful research tools that can enhance medicine and public health. The "social" power of biologic information should be considered, however, before any biomarker data are collected or used (2).

Some concerns associated with human biomarker research stem from misconceptions of investigators and the general public about the nature of biomarker research. An important misconception is that direct access to biologic material gives the impression, if not the reality, of being closer to the "truth" than studies using subject self-reports, environmental exposure measurements, or record review as key data sources. In some instances, biomarker data may be the most valid information; however, it can be subject to measurement, analytic, and interpretative errors. Even when biomarker data are valid, there is a range of problems in interpretation and in the use of the information that can significantly affect participants in research. From this, many observers have voiced concern that the information derived from biomarker research may be improperly used or have disastrous and unanticipated effects on study subjects, or segments of society, or both (2,3). Such potential misuse, however, is no reason to abandon this research. Rather, it should be seen as an alert to scientists and others concerned about biomarker research to take an active role in guarding against potential problems.

In this article, we will review the process of conducting research on human biomarkers and address the ethical issues that arise at each step in the process. Our goal is to illustrate some potential problems and stimulate dialogue among scientists on approaches to prevent them.

Design of Studies

The temporal design structure of biomarker research is important for identifying human subject issues. Therefore, as preface to the discussion of ethical concerns, it is useful to describe the three temporal types of study design: contemporary, future, and retrospective studies.

Contemporary studies are those in which the specimens are collected and assayed and the results disseminated within a relatively short period. These may be transitional (i.e., studies that validate a marker in the laboratory and in the field) or etiologic studies (4,5) in scope, and cross-sectional, case-control, or case-cohort in design.

Future studies are those that are either targeted or open-ended. In a targeted study subjects will be recruited over a long period and specimens may be stored or banked for years. The actual study purpose and, hence, the assays to be conducted are, however, known. In contrast, an open-ended study is one wherein specimens are banked because it is believed to be a good idea and a unique resource. Individual research projects will, however, be determined years after the actual specimen collection.

Retrospective studies have characteristics of both of these other types. They involve finding a bank of collected specimens, possibly collected for purposes other than the research originally anticipated, and linking specimen assay results with some health outcomes. For example, the JANUS bank in Norway has been collecting blood specimens for cancer research since 1973 (6). Suppose a series of specimens from 1973 to 1978 were assessed for a certain marker and then all those subjects were traced today for their health status with the use of Scandinavian cancer registers. Although the specimen collection was performed long in the past, the assays and linkage of assay results to cancer would be conducted in the present.

Each of these three types of study designs may raise certain ethical issues peculiar to it. Where these occur, they will be highlighted in the subsequent sections.

Subject Recruitment and Informed Consent

Subjects will be attracted or recruited in ways that can have ethical implications. This is particularly true if subjects are deceived or coerced into participating in a study or are given false expectations (e.g., we can tell if you are sick or well) with respect to the value of the study to the participant. For example, a researcher can coerce a potential subject directly (e.g., you may lose your job if you don't participate) or by implication. Communicating false expectations or using pressure are patently dishonest and unethical. It is unlikely that such deception or coercion would be overt, rather it would be more subtle and difficult to detect.

During the recruitment of study subjects, the investigator, as a matter of course, should clearly inform the subjects of

the intent and activities required for participation and of possible side effects. At least for federally funded research (e.g., 45 CFR Part 46), and as a matter of currently accepted practice in most other research, the collection of biologic specimens requires that subjects be told, in lay language, of the purposes and risks of a study, and the uses to which the specimens will be put, as well as other information. More and more peer-reviewed journals require statements by authors attesting that subjects were fully informed and participated voluntarily in the research.

Ensuring that each subject understands the implications of participating in a study is difficult and there is no simple formula for developing consent forms. Informed consent documents vary in length and complexity. Some are short recitations of general concepts. Others are detailed packages, indicating specific test risks, types of results, and notification that will occur. At present, there is not a standard practice for the degree of specificity required in informed consent documents. For contemporary studies, those in which the specimens are collected and the results are analyzed within a short time frame, practices may vary but the issue of results notification is more clear cut than for future or retrospective studies. Usually in contemporary studies, the subjects are known and they can be easily notified of results. With future or retrospective studies, this notification is more difficult.

A number of questions have arisen about the extent to which the investigator must go to inform the subject of unknown or unplanned use of specimens for past or future research. A question continually posed by researchers asks whether or not specimens collected for one purpose can be used for related or for distinctly different research. For example, may blood specimens banked in a cardiovascular study be used to look for cancer markers? Additionally, in some cases, specimens were collected and banked before the Belmont Commission's report of 1978, which set the stage for current human subjects practices (7). What is the responsibility of researchers using pre-1978 specimens to inform subjects who participated in studies prior to 1978? In general, what is the long-term responsibility of the researcher, or the research institute, or agency, or all three to keep the subjects informed of the use of their specimen(s)? The answers have not been clearly delineated for retrospective studies. Different agencies or institutions have widely different practices.

When subjects are recruited, the researchers should inform them of the risks and benefits of participation; detail the study activities; and describe, in general terms, any possible use of data in the future. Nevertheless, questions will remain about unspecified future uses of studies. What are the limitations of conducting additional analyses which are unrelated to the original study purpose?

Some researchers may feel hamstrung by human subject constraints that prohibit performance of additional assays on banked specimens. Some agencies permit this practice, others do not. A logical followup question is: Are the rights of subjects disregarded when unspecified assays are conducted on specimens collected for another purpose? This is an arguable question. The cutting edge of the ethical issue may be more along the line of what should be done when results of these additional assays are obtained. This will be discussed in a subsequent section.

The banking and use of specimens also raise the question of ownership of specimens. Who has legal ownership of specimens or the products of specimens? The case where a clinician used a patient's specimens to develop, patent, and profit from a cell line illustrates how these matters are still unresolved (8,9). Other questions of access involve whether other scientists or even nonscientific interests, such as insurance companies or employers, can obtain access to banked specimens.

Privacy and Confidentiality

Biomarker information about individuals has been useful in individual and group quantitative risk assessments (10,11). This use has been described from the vantage of the clinician and researcher, and the information is gathered with the consent and concurrence of the subject. The subject consents to provide the specimens and corollary demographic and risk factor information, and hence, cooperates in the specified research. The subject generally does not consent or imply consent to distribution of the data in a way that identifies him or her individually to any other parties, such as employers, unions, insurers, credit agencies, lawyers, etc.

Dissemination or revelation of results beyond the explicit purposes for which specimens were collected intrudes on subjects' privacy. Inadvertent labeling of a subject as "abnormal" or as "in the extremes of a distribution of marker assay results" could have a potentially deleterious impact on the person's ability to obtain insurance, a job, or credit; it also could affect the person socially. The psychological impact is virtually unknown. Thus, as Nelkin and Tancredi (2) note, some union leaders are concerned that workers will bear a "genetic scarlet letter" that they will become "lepers" or "genetic untouchables."

Although the records of government-sponsored or funded studies will be maintained according to the Privacy Act of 1974 (PL93-579), this does not ensure that records will never be disclosed. Title 5 in the Code of Federal Regulations describes the conditions under which records held by the federal government can be disclosed (5CFR 297.401). These are shown in 12 situations written into the Privacy Act that permit releasing information in identifiable form:

The records are necessary to protect the health and safety of other persons.

A researcher uses them only for statistical research.

Agency officials, or groups working with an agency, need the records for uses compatible with the purpose for which the information was collected.

The records are needed by agency personnel, who need the records in performance of their duties.

The release of records is required by law.

The Bureau of Census needs the records for census or survey work.

The national archives needs them for historical purposes.

Either house of Congress requests an individual's records.

The comptroller-general needs the records for the General Accounting Office.

A court orders the records.

A consumer reporting agency needs the records to assist the federal government in collecting a claim owed the government.

The records are requested under the terms and conditions of the Freedom of Information Act, and their release would not invade an individual's privacy.

These conditions apply to most federal record systems. Confidentiality may be more assertively protected in studies sponsored by agencies within the Public Health Service if the investigator obtains a special clearance, provided by Section 308(d) of the Public Health Service Act [42 U.S.C., 242m(d)], which bars disclosure to any party other than the subject.

In studies conducted by academic, business, or labor researchers, standard practices to maintain privacy and confidentiality are generally followed (12). In these situations, however, there is more leeway to interpret the degree of confidentiality than with federally conducted research since the practices are voluntary.

Interpretation and Communication of Test and Study Results

Researchers have a responsibility to interpret biomarker tests correctly--not to let themselves be deceived by the extensive variation in genetic and biochemic individuality. The inherent variability among individuals influences the interpretation and communication of biomarker data. Motulsky (13) has aptly described this variability:

Human physiognomy is unique and no two human beings except identical twins are alike. The involved genes remain unknown. Remarkable genetic individuality also exists for red cell and tissue cell (HLA) groups, in enzymes and proteins. Enzyme variation usually is associated with variable enzyme levels in the normal range, so a person's exact activity level for a given enzyme (i.e., high normal, average, low normal) may be genetically determined. Most enzyme variation will lead to differences in the speed of breakdown of various substances. Protein variation may lead to differential binding of foreign substances.... Variability at the DNA level is more striking. Frequent differences occur at the individual nucleotide level (every 500 nucleotides), as do size variations of longer stretches of DNA (minisatellites). Most such DNA variants are phenotypically silent but often can be used as markers for closely linked gene loci that specify proteins that have physiologic, biochemical, or immunologic effects.

This natural variability makes it essential to know the range of biomarker values in a normal population. Depending on the biomarker, the range of normality can be quite extensive. A healthy level for some individuals may indicate a health risk for others. For example, it is well known that the cholinesterase level in subjects not exposed to organophosphorus insecticides covers a wide interindividual range (e.g., plasma; men, 0.44-1.63 pH/hr; women, 0.24-1.59 pH/hr) (14).

Hence, a 25% change in the group mean may mask a 50% decrease in a few subjects.

Although many studies involve biomarkers for which a normal range has not been established, the researcher should nonetheless provide some perspective on results for each subject. This could be accomplished by providing subjects with their results, indicating the group mean and range and those for any comparison group, and explaining the lack of a known normal range.

Interpreting studies that involve biologic markers and relaying the results to the study group pose a number of other dilemmas. One such dilemma arises because interpretation of results is often influenced by the tension between group effects and individual effects (15). Research data may yield information on group risks but not indicate individual risk. This dilemma is characteristic of epidemiologic research and predates studies using biologic markers. One of the major potential advances of molecular epidemiology is the ability to obtain specific information that may be predictive of risks to individuals (11,16). This ability is not new to epidemiologic research (17), but the exquisite sensitivity of individual risk determinations based on gene assessments puts researchers and society in difficult positions with respect to interpretation of results when markers are not yet validated. The traditional paradigm that epidemiologic research pertains to a group leaves individual study subjects at a loss regarding the meaning of results for them. Subjects may be able to learn about significant group risks but may not be able to obtain any meaningful information about individual risks unless investigators have developed risk functions that will calculate individual risk. Still, institutional review boards often require that study subjects receive their own test results along with some explanation or interpretation as soon as the individual results are available. Epidemiologists have not yet agreed about the language for these communications.

The discordance between the meaning of group and individual effects may be tempered if the limitations of the biomarker research are clearly communicated to the subjects prior to their participation and reinforced during the explanation of the results. Individuals participating in a "research" study may misinterpret the purpose of the study and believe it is a health study and the results will tell them whether or not they are "all right." Clearly, this misconception may frustrate the subjects and researchers in studies that assess only a marker's validity or that provide information useful in an epidemiologic, rather than a clinical, sense (18). Nevertheless, some biomarker studies may identify potentially relevant clinical findings.

In most biomarker studies, typically only one or a few markers are used because of the wide variances in human biomarkers. A single marker assay rarely should be interpreted in isolation. On an individual basis, the findings should be confirmed by a repeat test given at some later date. Other confirmatory studies should be sought for group results. When possible, batteries of markers may provide a fuller picture than would be seen with one or a few markers (15).

In studies that compare putatively exposed and nonexposed individuals, the results may indicate that exposure is

continuing and that there is an exposure- response relationship. Such a finding may trigger the need for the researcher to address this fact so that subjects can take preventive or remedial action.

Any positive study using markers that are considered biologic changes capable of being part of a disease process should trigger consideration of the need for medical surveillance. Although this is a prudent policy that may involve surveillance of some subjects with false-positive test results, it will at least allow true-positive subjects to be candidates for early intervention or therapy. Short of that, researchers still should make a strong effort to describe the limitations of biologic markers, to counsel subjects and, in some cases to provide the subjects' personal physicians with information regarding the state of knowledge about the markers.

The complexity and uncertainty (regarding disease risks) of biomarker data may be why researchers and agencies have been reluctant to communicate biomarker test and study results. Minimal disclosure of results is furthered by the fact that many biomarker findings have no clinical interpretation and because of anxiety about misinterpreting issues conjured up by terms such as "mutation," "gene rearrangement," "DNA adducts," or "at increased risk" (15).

Nonetheless, some agencies require complete and full disclosure of all test and study results to subjects (e.g., 45 CFR Part 46). This is intended to be done in clear language, understandable to the lay person (study subject), and with an interpretation about what it means to them regarding risk and the need for followup. Subjects generally want to know if "they are all right." Often biomarker research is not designed to answer that question. This caveat needs to be made clear in the informed-consent procedure and then reiterated in the result dissemination. Some subjects will be in the extreme of distributions of results, suggesting higher exposure, increased risk, or the existence of some inherited characteristics that could put them at risk given a particular exposure. Drawing such conclusions, however, is often distressing to scientists who believe the data cannot be interpreted or summarized to that extent. Key in these deliberations is the need to think not just as a scientist but also as a clinical or public health specialist and as an advocate for the subjects. Thus, it may be useful to reflect on whether the findings could indicate a possible individual or group risk. Put another way, researchers should ask themselves if they were the subjects, what would they want to know about the results. The reflections should however, also include consideration of how the information can be misinterpreted. Such thinking can be considered paternalistic decision-making, which has come to have negative connotations indicating disregard, be it well intentioned or nefarious, of a person's right to self determination. A possible solution is to just tell subjects what is found together with all the uncertainties. This generally will suffice for noncontroversial research. For controversial research, a panel of representatives of the involved and affected parties may be needed to come to a consensus on the interpretation or at least on the range of interpretations and on possible followup actions. For these types of situations, the best approach may be the involvement of these parties at the conceptualization of the study and throughout the process, rather than only at the dissemination phase.

Communication to Control Subjects

Interpretation of biomarkers also needs to be assessed in terms of possible background of the biomarkers in the general population. Since biomarkers may represent exposures from various sources and by various routes, a baseline in people not exposed by the route or source of interest is important. For example, in a study of dioxin, serum levels were measured in the unexposed referent population. These data were invaluable in determining that, although the referent population was not exposed to occupational sources of dioxin, they all had low serum levels of dioxin, presumably caused by low-level environmental contamination (19). Although it is still unresolved whether the low levels of dioxin in adults cause obvious adverse outcomes, control subjects will require some interpretation of what the data mean.

Similarly, in a study of hospital workers exposed to ethylene oxide, nonexposed control workers were found to have hydroxyethyl hemoglobin adducts (20). This means that other exogenous and endogenous sources of hydroxyethyl moieties needed to be considered, and subjects were apprised of this fact.

Responsibilities for Action

Studies that indicate excess frequency of exposure markers may obligate researchers or authorities to address the source of exposure. For researchers, this may involve, at the least, speculation as to the nature of the source. For authorities, it may involve investigation and efforts to control exposure.

For markers of effect, the actions to be considered may be primary or secondary preventive ones. For example, a cytogenetic finding such as increased sister chromatid exchanges in a group of individuals, may trigger the kinds of environmental controls needed to address exposure even though these are nonspecific-effect markers. The markers may also trigger ongoing medical screening or monitoring for disease. If the marker is intermediate in the disease process and still reversible, interventions, such as chemoprevention, may be considered (21).

Markers of susceptibility, such as a P450 genotype, are the most problematic with regard to what actions can be taken. Markers of susceptibility can be used in research as effect modifiers indicating there is interaction of two or more variables. Routine monitoring or testing for markers of susceptibility are not intended to diagnose manifest symptoms of illness or dysfunction; rather they are intended to discover the truth behind appearances, that is, to detect conditions that are latent, asymptomatic, or predictive of possible future problems (2). The use of these tests in job placement, for example, can be discriminatory per se, as well as when they are correlated with various demographic characteristics. This can occur when a marker's frequency is predominantly found in ethnic or racial groups that historically have been discriminated against. Using biomarkers for genetic screening can create various ethical problems, and the many cautions have been discussed elsewhere (22-25).

Dilemmas for Researchers

Scientists like to think of gathering and interpreting data as being independent from the social and political context; but this is not always possible, especially for data from biologic monitoring of workers or community residents (for example, near a hazardous chemical source). In these and other instances where there are current controversies over health risks, communicating the results of such data cannot be separated from the use of the data (3). Dissemination of risk information from biomarker studies or routine biomonitoring can have implications for citizens' and employees' rights to privacy; confidentiality; and nondiscrimination with respect to employment, insurance, medical removal protection, and acceptability for loans. Hence, researchers must be aware of the social power of biologic information (2).

When test and study results are disseminated, subjects not only want the results to be interpreted, they may want recommendations on what to do about them. These recommendations may range from obtaining medical screening or surveillance to seeking environmental or behavioral changes to avoid further exposures. Although researchers or their research institutions generally have limited responsibility in implementing or obtaining followup activities, they may have a responsibility to point out relevant issues.

New scientific developments will exacerbate many of the issues discussed here. The obstacles to understanding associations between genetic predisposition and disease are slowly evolving as the use of synthetic probes, the polymerase chain reaction, and automated DNA-sequencing machines increase the efficiency and lower the cost of large-scale use of assays in human populations (22). With these innovations, the temptation to use tests or markers before they are validated (26) may increase. For population studies, validation means not only laboratory validation to see if the test works but also epidemiologic validation (26). This involves determining the predictive value and characterizing such features as the range of normal, background prevalence, variation by age, race, sex, etc. There is also the temptation to believe that finding a genetic polymorphism may explain human behavior and disease. This reductionist attitude occurs among scientists who find genetic explanations more attractive than complex "unmeasurable" social explanations (27). The debate between nature and nurture is likely to continue even though, as Keller (28) notes, "Most responsible advocates are, of course, careful to acknowledge the role of *both* nature and nurture, but rhetorically, as well as in scientific practice, it is 'nature' that emerges as the decisive victor." This shift to a genetic versus environmental explanation is evident in the debate over genetic susceptibilities of workers. The Office of Technology Assessment (22) has described the trend and provides a balanced appraisal of the roles of genetic and environmental factors.

Molecular biology has enhanced the traditional determination of "predisposition to disease" (previously based on physical examination, family history, and lifestyle habits) by seeking out and finding genes or markers associated with disease. Individuals found to have the gene or the marker can then be identified, sometimes with near certainty, to be candidates for disease. Often, predisposition only manifests in disease when there is an accompanying environmental insult, e.g., toxic substances, viruses, or other disease. The influence of the environment, however, remains the wild card in most cases, because possession of the genetic predisposition alone may be insufficient to cause disease. It is likely that for some time modern science will be more successful in identifying the genes and the markers than in identifying the environmental agent(s) necessary for activation of the predisposing genes.

Shifts in this debate in one direction or the other can have large influences on political and social responses to divergent problems such as disease, homelessness and behavior (28).

The capability and widespread use of the technology to assess biomarkers may result in the identification of population subgroups at increased susceptibility or risk of disease. Hornig (29) has concluded that the central policy question is: how should the variation in the sensitivity of groups and individuals be taken into account in environmental laws and regulations? This question assumes an ease of determination and accuracy in determining the existence and nature of sensitive subgroups. However, scientific uncertainties limit the identification of sensitive subgroups and individuals. Moreover, a susceptibility marker is only a statistical indicator whose predictive value depends on the frequency with which those with that marker develop the expected disorder. Often, as in the case of ankylosing spondylitis, the arthritic condition linked to *HLA B-27*, many more persons positive for the gene remain disease free than actually become ill.

Implications of Biotechnologic Developments

The techniques used in the assay of biologic specimens are being developed in various disciplines such as molecular biology and genetics, clinical and analytical chemistry, and toxicology. Coincident with the use of human biologic materials for public health research are efforts to use these materials for profit. This raises important ethical, legal, and economic issues. The use of human specimens in biotechnology raises questions that have not been answered in previous public policy deliberations. The Office of Technology Assessment (9) identified the following problematic questions:

Who owns a cell line--the human source of original tissues and cells or the scientist who developed the cell line?

Should biologic materials be sold, and if so, what are the implications for equity of distribution?

Should disclosure, informed consent, and regulatory requirements be modified to cope with the new questions raised by the increased importance and value of human biologic materials?

These are novel and complex questions that have difficult answers. Currently, biotechnology is not specifically regulated. Moreover, new forms of collaboration between academe and business are becoming more common. The traditional open exchange of information is giving way to more secretive and proprietary behaviors. There is a need for a broad-based ethical review of the issues related to these biotechnological endeavors.

Conclusion

In conclusion, awareness of the social power of biologic information presents a tension for the research scientist using

human specimens and biologic markers. This tension has been described in the publication, "On Being a Scientist" by the National Academy of Sciences (30). Three themes are addressed in the report: the relationship between the "objective" and the "subjective" in scientific research, the social mechanisms within science that contribute to its authenticity; and, the wider social responsibility of the scientist. Although these questions have characterized science for centuries, they have particular relevance to the human subjects issues in specimen collection, analysis, and interpretation. Such research requires that scientists be both objective and subjective. They must be objective in determining the rationale for the research, in designing it, and implementing it. This includes accurate portrayal of risks and benefits to potential subjects during the recruitment and consent phase and in interpreting and communicating results. Researchers also need a certain amount of subjectivity in this process to adequately address concerns from the vantage of subjects and other interested sectors of society and to provide recommendations for preventive, remedial, or clinical action. The report "On Being a Scientist" (30) rejects the notion that objectivity is the result of eliminating subjectivity. Rather, it is the result of authentic subjectivity that is the result of researchers being attentive, intelligent, reasonable, and responsible with regard to the potential impact of their work (30). With this as a framework, many issues still need to be resolved. These include the use of specimens for purposes for which they were not collected, the extent of reporting back results, ownership of specimens, use and interpretation of results. These cannot be left solely to ethicists and institutional review boards; scientists need to participate in the discussions and contribute their views and concerns.

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