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Report balances privacy versus whole genome sequencing

Misuse of information is addressed

Medical and electronic data advances in the 21st century have made it possible to determine the entire DNA sequence of any individual on the planet. The first question that many bioethicists ask is, "How do you protect individuals' privacy from the misuse or unauthorized use of this information?"

The goal is to reconcile privacy with the enormous public benefit that whole genome sequencing has to offer, says **Lisa M. Lee**, PhD, MS, executive director of the Presidential Commission for the Study of Bioethical Issues (PCSBI), which was created in 2009 by executive order to study and promote policies that ensure the ethical conduct in research and health care delivery.

The PCSBI, chaired by **Amy Gutmann**, PhD, president and professor at the University of Pennsylvania in Philadelphia, held public meetings to discuss genome research and privacy for more than a year. In October 2012, the commission issued a report titled, "Privacy and Progress in Whole Genome Sequencing." The report addresses privacy concerns in the new era of a readily available technique for determining the complete sequence of individuals' DNA.

"The commission has crafted 12 recommendations, calling for strong baseline protection for privacy while promoting access and sharing of data," Lee says. "We're really interested in ensuring that many people feel safe in sharing their data; we need data from an enormous number of individuals to move this research forward."

Trust is essential for the research to progress, and this means improved data security and access to databases, Lee adds. *(See summary of 12 recommendations, page 136.)*

"The most important piece is a fully informed consent process," Lee says. "People who are participating in whole genome sequence research and those having research done in a clinical setting need to know what it is they are signing up for."

Participants should know what whole genome sequencing is, what it will

do for them and their family members, and they should know how the information will be used in the future. Also, they should have some say in the decisions for using genome data, she adds. *(See PCBSI and informed consent, p. 135.)*

Commission members acknowledged in various discussions about whole genome sequencing and privacy the way this issue has evolved in an era of rapid adoption of new technology. Privacy remains a value to society, but the lines between private and public have changed over time, according to Gutmann, who chaired a PCSBI meeting on the topic, held Aug. 1-2, 2012, in Washington, DC.

"And technology certainly has contributed its fair share to those shifting lines," Gutmann says.

Technology also can be used to influence public opinion about privacy, according to an expert who spoke before the commission at the August meeting.

"We can craft new technology to shape how society might think of our privacy as we go forward," says **Latanya Sweeney**, PhD, visiting professor and scholar, computer science, and director of the Data Privacy Lab at Harvard University in Cambridge, MA.

"Last year PricewaterhouseCoopers estimated that the sharing of medical records beyond the care of the patient was a $2 billion market. The result on society is a belief that privacy is dead. There's just too much information out there," Sweeney explains. "On the other hand, once collected, these data, my data, your data become closely guarded private assets of these companies."

The goal from a bioethical perspective might be to use new technologies to help society enjoy both privacy and utility of data, she notes.

"And I've had a lot of success in this area," Sweeney says. "It includes ways of assessing re-identified risk in data, methods for sharing data under the HIPAA statistician provision and so forth."

Harvard University has two living labs that could provide best practice models for finding a balance between technology, sharing information, and individual privacy. One is the MyDataCan lab, in which the public can assemble and control their own data. The other is the Data to Science project, in which people donate data to science after death.

"This approach combines data that's otherwise trapped in silos, giving the individual the most complete copy of information about themselves," Sweeney says. "And it adds transparency and knowledge to data-sharing arrangements."

Both MyDataCan and Data to Science labs have a privacy guarantee that says the holders of the data cannot view the data. The MyDataCan information is doubly encrypted, with Harvard holding one key and the other maintained by the individual. The Data to Science information cannot be viewed until the individual dies, she explains.

"[W]e believe these kinds of living labs will provide benefits and utility to society and begin to establish new norms for privacy expectations," Sweeney says.

There should be mandatory data security and information protection standards to fulfill the

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obligations of public trust in genetic research, according to **Sonia Suter**, MS, JD, a professor of law at George Washington University in Washington, DC. Suter also spoke at the August PCSBI meeting.

"Perhaps [we should] even require that the information really is used for the public good," Suter says. "That's a vague notion, but some sort of promise to the people that when they're giving up a little bit of privacy rights that they're doing it for the public good since altruism motivates people to participate in research."

Security protections should extend to a prohibition on inappropriate re-identification of samples and inappropriate uses of genetic information, she adds.

"And I think it's really important to have laws that prohibit the surreptitious kind of sampling and analysis that is allowed in most states, or isn't prohibited," Suter adds.

From a legal perspective there are two other things research institutions can do to improve their handling of privacy issues:

- **First:** "To acknowledge the needs for research while giving people some control over their samples and their information but not full control," Suter says. "We might think about having a kind of general consent for research with some options to opt out of future research and particular categories of research."
- **Second:** "And then I also think it's really important to ensure that people have full understanding of the limitations of privacy protections in this area; that while there are efforts to maintain security of the data that it's not entirely failsafe," she adds. "One of the greatest risks of participating in this research is the fact that there are privacy risks and people should be aware of that."

Whole genome sequencing provides some unique health care and research opportunities, and it generates a lot of interest in the general public, Lee notes.

There are strong communities of people with genetic conditions who are extremely interested in sharing their data and having researchers use their data to learn about their condition, Lee says.

"We have groups of people who pull together on the Internet and want to use their data and have researchers use it to advance science around their condition," Lee says. "When we talk about creating a place where we can promote data access and sharing, we want policies in place where data can be shared safely, and those policies also protect people who don't want their data shared."

The key to a whole genome sequence research policy is that it recognizes the balance needed between the use of this technology, the benefits to society of this research, and the need for safety among individuals who contribute their genetic data to the research, Lee says.

"We want to create a safe base where people can put their data, and we can make progress," she explains. "But unless we create that safe place, solid barriers of security, people won't want to participate." ■

Consent is a major focus of commission's report

IC process is most challenging

Whole genome sequencing research raises important informed consent issues for IRBs and investigators, and the recent report by the Presidential Commission for the Study of Bioethical Issues (PCSBI) addresses these in its recommendations.

"The specific informed consent recommendations the commission made have to do with two important pieces of consent: One is the consent process and the other is consent forms," says **Lisa M. Lee**, PhD, MS, executive director of the PCSBI.

"The commission recognizes these are two different things, and the easy one is the informed consent forms," she adds. "We recommend OHRP [Office for Human Research Protections] or another agency specifically provide guidance to researchers who do whole genome sequencing about what should be included in consent forms."

This recommendation stems from researchers telling the commission that they are not sure what to include because this type of research is very complicated, Lee notes.

For example, how should researchers describe the safeguards in place to protect whole genome sequence data from being re-identified through some future advances in technology?

Whole genome sequence data can be stripped of traditional identifiers, but it remains unique to one particular person. These data would be confidential so long as it remains de-identifiable. So informed consent could be waived by an IRB, according to the Common Rule, the PCSBI report states.

"The Common Rule states that data and specimens collected in the clinic, when stripped of traditional identifiers, can be used in research without consent," the report says. "Because consent requirements differ in clinical and research settings,

researchers could theoretically seek out data and specimens collected in the clinic to bypass the more involved research consent requirements."

However, the commission states that it does not condone researchers circumventing IRB approval by seeking out clinical data and specimens for use in research when they could not otherwise obtain IRB approval.

Evolving technologies have made the concept of de-identified data fluid in the public's mind, the report notes.

"If data becomes readily re-identifiable, and some people think that would be possible soon, then we're dealing with a different set of circumstances," Lee says.

The commission's report suggests that even when data are being accessed and used with informed consent, the privacy of individuals should be well protected by the researchers using the data.

In general, the informed consent form should include a definition of whole genome sequencing, how the data will be used, stored, and analyzed, and whether the participant would have any say over that use, and whether incidental findings will be returned to individuals or the participant's physician, Lee says.

The report also notes that some informed consent documents acknowledge that absolute privacy cannot be guaranteed and that IC policies will evolve as the public's notions of privacy evolve and change.

The informed consent process is an even more complicated issue, and experts have proposed a variety of methods for handling it, she says.

"There are many other types of consent processes being considered now with these studies," Lee says. "Many folks are experimenting with things like dynamic consent where people who are participating are contacted or re-contacted based on new studies and opportunities for their data to be used."

Others are considering the broader issue of how people want their data used and offering them opportunities to opt out of research at the time the specimen is collected, she adds.

"One suggestion from OHRP and the ANPRM [Advanced Notice of Proposed Rule Making] is that people have control over what kind of study their data can be used for, and they can pick that at the outset," Lee says. "The commission studied different types of consent, evaluating what works and taking a hard look at what kind of consent people want and what works; the commission recommends that they be studied." ■

PCSBI makes these 12 recommendations

Focus is on informed consent

The Presidential Commission for the Study of Bioethical Issues (PCSBI) has made these 12 recommendations for how to better develop public trust and protect privacy in the era of whole genome sequencing in research:

1. Establish clear policies regarding data access.

Sponsors, research institutions, database owners, and policy makers should make clear policies defining what type of access is acceptable in using whole genome sequence data. Strong baseline privacy protections are necessary to ensure safe sharing of genetic data.

2. Federal and state governments should ensure a consistent floor of privacy protections.

Policies should prohibit whole genome sequencing without the consent of the individual from whom the sample came. Full informed consent should be obtained at the outset of diagnostic testing or research.

3. Funders of genome research, database managers, and policy makers should ensure data protection.

Data protection would be enhanced by having all persons who work with whole genome sequence data to do the following:

- be guided by professional ethical standards related to privacy and confidentiality;
- held accountable to laws and regulations that require specific remedial or penal measures in the case of lapses in data security.

4. Funders, research managers, database owners, and policy makers must outline acceptable access to identifiable whole genome sequence data.

Whole genome sequence data should be stripped of traditional identifiers whenever possible. Exceptional circumstances might permit law enforcement or defense and security to gain access to biospecimens for non health-related purposes without consent.

5. Federal agencies should invest in initiatives to ensure all parties with access to whole genome sequence data comply with regulatory and other data privacy and security requirements.

6. Use robust and workable consent processes.

The IC process should provide research participants with information about who has access

to their whole genome sequences and how these data might be used in the future. Their specific preferences should be noted when the samples are obtained.

7. OHRP or another federal agency should write clear and consistent guidelines for IC forms in genetic research.

The PCSBI recommends that IC forms contain:

- descriptions of whole genome sequencing and analysis;
- information about how data will be used in the present study and how data might be used in the future;
- explanation of how much control the individual will have over future data uses;
- definition of benefits, potential risks, and a statement that acknowledges unknown future risks;
- statement of what data and information — if any — might be returned to the individual.

8. Make individuals aware of likely incidental findings.

Researchers, clinicians, and sponsors should make individual participants aware of any incidental findings that are likely to be discovered during the whole genome sequencing. The IC should specify how and to whom to communicate these findings.

9. Genetic research funders should support studies to evaluate frameworks for offering the return of incidental findings.

Funders should investigate genetic material contributors' preferences and expectations.

10. Funders, clinical entities, and others in the commercial sector should facilitate a safe exchange of information between genomic researchers and clinicians.

Information exchanges must maintain data protection safeguards to facilitate whole genome sequence and health data sharing.

11. Policy makers should promote opportunities for the public to benefit from the research.

The research community and policy makers should promote opportunities for the exploration of alternative models of the relationship between researchers and participants, including participatory or collaborative relationships.

12. The federal government should invest in whole genome sequencing to benefit all people.

Government investment in genomic research has provided ample public benefit through improved health care, and this work should continue to benefit all members of society. Researchers should include individuals from all parts of society in their studies. ■

COMPLIANCE CORNER

Complaints or just seeking answers?

Consider caller's emotions

Human research protection programs (HRPPs) often must balance the need to handle research complaints with the goal of conducting fair and reasonable investigations into any potential problem. HRPPs also must use staff time efficiently and not get bogged down in disputes that clearly are not pertinent to protecting research subjects, an expert says.

All research-related complaints at Vanderbilt University in Nashville are handled by the institution's human research protection program, regardless of their source, says **Jan Zolkower**, MSHL, CIP, CCRP, regulatory compliance manager at Vanderbilt University Human Research Protection Program (VUHRPP).

"Once we get these complaints we substantiate them and we conduct an investigation," Zolkower says. "We match up corrective action plans compared to the level of the situation it addresses; if it's a minimal risk, we do a lower level of investigation."

All of the institution's informed consent forms give subjects a toll-free number to call if they have any concerns about their rights as a research participant, and that number leads them to Zolkower.

Zolkower divides complaints in two categories: contacts and complaints. Contacts are calls, emails, or other communication that is not directly related to a research study's compliance, conduct, or staff. Complaints are issues that are related to the research study and staff and that need to be investigated further.

Some calls can fall into either category depending on the caller's level of emotion and whether it appears to be a legitimate gripe, even if it isn't directly research-related. Here are some examples of contacts and complaints:

- **Contacts:** Some of the most common calls are from research participants who have not received their compensation checks, Zolkower says.

"I had a person call me last week who had not gotten the compensation but had participated in the study two days earlier," she explains. "We tell participants it can take up to four to six weeks to get their compensation; that one was classified as a contact — not a complaint."

Zolkower also receives questions about a study from research participants. If these are specific questions about the study and research, she'll refer the caller to the study's investigator. If they involve general questions about the study, such as direct benefits or risks, she will look at the study's informed consent document and repeat the information in that.

"I count those as contacts," she says.

Another example of a contact is the call in which a research participant needs help with something that is not directly related to the research.

For example, Zolkower heard from a participant who had received her research compensation check in the mail but didn't have a bank account and could not get the check cashed.

"She needed a mechanism to cash it and wanted to know what I could do in this situation," she says. "Ultimately we worked it out with the study staff by having them provide another mechanism for providing her compensation. It could be a gift card instead of a check."

• **Complaints:** Contacts can be filed as complaints, depending on the level of distress of the caller, Zolkower says.

Complaints also are calls that directly relate to a study investigator or staff's behavior or to some problem that occurred during the study or as a result of the study. Studies that involve genetic testing sometimes result in calls about subjects' individual genetic results, even when the informed consent document explicitly states that individual results cannot be given to participants, Zolkower says.

"We had a gentleman who participated in a study on the prostate," she says.

"The study looked at markers for the cancer and the man went on to develop prostate cancer a couple of years later," Zolkower adds. "He called to ask us for information to see if his cancer could have been detected sooner, but the informed consent document clearly said the results couldn't be provided."

The study's data had been stripped of all identifiers and could not be tracked back to individual participants.

"Fortunately, most folks who call get our phone number from the consent form," Zolkower says. "When they call me, they will have that informed consent form in front of them, so I just ask for the investigator's name and the title of the study."

When she receives calls about personal data results, Zolkower routinely tells the caller she'll look into the issue and return the call within 24 hours. She checks the study's electronic information, including the signed consent form to make sure study staff provided all information according to what the IC form states. Then she calls the participant. *(See story on handling study complaints, below.)*

If the IC form said that no results would be given, Zolkower might explain this by saying, "When you agreed to participate, you were told the results would not be provided, and this is what we agreed to up front. So, unfortunately, I am not able to provide research-related results to you."

She might also add: "In genetic testing, the sample has been stripped of all identifiers so there is not even a mechanism for us to go back and check your sample."

Most of the time, callers will let the issue go when they hear these explanations she says. ■

Tips for handling study complaints

Investigate, validate, correct

Research institutions should make their complaint process as accessible as possible to researchers, participants, and others, an expert says.

"We have a suggestion box where participants and staff can submit anonymously, and we have a link to the complaint form under a participant tab on our website," says **Jan Zolkower**, MSHL, CIP, CCRP, regulatory compliance manager at Vanderbilt University Human Research Protection Program (VUHRPP).

Complaints can be submitted online anonymously or with the person's contact information for follow-up.

Research participants and others also can call Zolkower directly if they have a question or concern.

VUHRPP has a written procedure for how investigators and IRBs should handle complaints. Among the key responsibilities listed on the procedure are:

• Investigators must notify HRPP of any participant or other individual's research-related complaints, and they can report the complaints at continuing review unless there is a risk to participants or others.

• Investigators must report complaints that pose a risk to subjects or result in a potential change in the risk/benefit ratio of an unanticipated problem as soon as possible and no later than 10 working days after the investigator learns of the complaint.

• Investigators must cooperate with HRPP, make documents accessible, and respond to written requests within the designated time frame.

• HRPP will notify the assigned IRB chair or designee of the initial complaint.

• The IRB chair or designee may request revisions or additions to the planned investigation or directed audit activities.

• An IRB regulatory compliance analyst will collect as much information as possible when receiving a verbal complaint and complete the IRB Complaint Information Form.

• All written complaints are forwarded to the HRPP director and the research subject advocate for investigation.

• When a complaint is substantiated, the HRPP director will forward the complaint to the HRPP Process Improvement Team for further investigation.

• Complaints that involve sensitivity issues may be forwarded to the IRB Optimization Committee for discussion and recommendations.

• The investigation's results are reported to the HRPP director, and if the complaint is study-related, it's reported to the IRB.

• The regulatory compliance analyst forwards all determinations and/or recommendations to the HRPP director.

• The HRPP director may notify the IRB medical director when warranted.

• The regulatory compliance analyst will update the IR database, and records of the complaint and investigation will be kept in a separate file in the IRB office.

• The HRPP suggestion box is checked frequently and responses are given to known complainants.

When Zolkower receives an oral complaint, she takes these steps:

• First, the complaint is investigated: It's important to investigate the complaint with an open mind, she notes.

Sometimes what sounds like a clear-cut violation could turn out to be a misunderstanding.

For example, there was one case where a parent called to complain that his or her child had been enrolled in a research study through the school system when the parent had clearly returned the informed consent, saying he or she did not want the child to participate, Zolkower recalls.

"We made an appointment with the investigator, and I reviewed all documents for all children in this study," she says.

She saw the name of the caller's child, but there were no study data included, and the document said the parent had declined participation.

"In the spread sheet, all remaining data fields were completely blank while all the other data fields for other kids were completely filled in," Zolkower says. "The caller was convinced that their child had been interviewed, but the child could have talked with other children in the class who were in the study and knew what they had been told when they were removed from the classroom."

When speaking with people who are making a complaint, it's important to be careful and validate their experience, she notes.

"You are talking to someone who's very upset and passionate about what has happened," she says. "So be careful and validate, but do a thorough investigation so you can back up whatever answer you're giving."

In the case of the child and consent, Zolkower explained to the parent that the investigator's file contained no documentation to support that an interview had taken place; there were no case report forms or study forms with the child's name on it, and there was no study ID number for the child.

"The parent still was convinced that this had occurred," Zolkower says. "I said, 'If anything else comes up in the future that leads you to believe a study interview has taken place, then here's my contact information.'"

• Secondly, follow-up action occurs: When an investigation shows that a complaint is valid and involves study staff conduct, Zolkower will investigate, notifying the IRB director, associate directors, and chair of any findings. The IRB chair will review the complaint and findings and then determine if it should be discussed at

an IRB meeting.

"They make a determination of what course of action needs to be taken and what kind of corrective action plan needs to be implemented," Zolkower says. "I am there to provide details during the IRB meeting, if requested; they usually come up with a plan, and it usually begins with education to the principal investigator and study staff." ■

Ensuring trial compliance? There's an app for that

Apps provide real-time protocol compliance data

With the smartphone application market seemingly exploding with apps for just about anything, it's no surprise that clinical research is starting to get in on the action. Technology companies and academic institutions are working on research apps and other programs to assist with clinical trial data reporting.

"The Pew Research Center recently reported that 46% of Americans have a smartphone," says **Joel Hughes**, PhD, director of the Applied Psychology Center at Kent State University in Kent, OH. "It's very ubiquitous now, and will get greater and greater adoption. I see this as being a broadly applicable way to ensure adherence to protocol."

With millions of people relying on their smartphones for everything from email to checking the weather and even monitoring their home security systems, clinical researchers are seeing the benefit of using the devices to monitor research subjects and even determine the effectiveness of healthcare apps. Pew Research Center reports that 52% of smartphone owners have sought health information on their phones.[1] A quick check of ClinicalTrials.gov shows 45 registered trials that involve smartphones in some way, ranging from depression treatment to fitness, pain management, and medication compliance.

Hughes is currently using an iPhone app in a study to improve medication compliance in heart failure patients. The app gives Hughes and other researchers real-time data on patients' compliance rate. "When using an app, you know immediately what they're doing." Hughes says. "We know right away if they've dropped off the protocol."

Patients using the app can set up a customizable medication schedule that will remind them to take their prescriptions at the appropriate times. The program can give patients further instructions for their medical conditions, and can report the results to researchers in real time.

"You know right away what the patients are doing — you don't have to wait for them to come into the office," Hughes says.

Protecting privacy

Since many of the study patients do not have smartphones, the researchers provide the phones as an incentive for participation. Hughes said that while the IRB had initial concerns about providing smartphones, they have become more open to the idea. "We've made nine IRB applications [for providing phones], and they've always gone through," he says.

"I think the IRB is wary of anything they haven't seen before," he says. "Their job is to protect human subjects. With apps, there's more accuracy, a lower dropout rate, and immediate reporting of adverse events. We don't have to wait to hear from patients — they can tell us right now. Over time, the IRB became very receptive."

The biggest concern has been privacy, but Hughes and his team have found ways to make the devices more secure. "With any patient device, you want to make sure it's secure and HIPAA-compliant," he says. When patients enter their data in the phone apps, it's transmitted to the study server, de-indentified, and encrypted. "No one knows the patient's name or the medications taken, even if the information is de-encrypted," Hughes says. "You only know what button was pushed. It helps tremendously with security." And if a phone is lost, data can be erased remotely.

"Smartphones don't discriminate with access to care — nearly 50% of people in this country have smartphones," he says. "Age can be an issue — while usage isn't as widespread for the elderly, we do provide for them. As the cohort ages, access to smartphones will be surprising."

Hughes also sees clinical trials apps and software expanding to include even more data. "I think they will include a more graphical interface to report back to the clinician," he says. "For example, if the user is taking their blood pressure,

the numbers can immediately come back to the provider and the researcher. We can also push education to patients, including podcasts that will show them exactly what they need to do."

But while Hughes sees big possibilities, it's still all a matter of getting there. "There are many exciting possibilities, but it's technologically challenging and expensive," he says.

Reach a large audience by texting

Smartphone apps aren't having all the fun in clinical research — text messaging is also being investigated in research as a way of effectively reaching a large population. **Brian Mustanski**, MD, associate professor and director of the IMPACT LGBT Health and Development Program of Northwestern University in Chicago, is leading a trial to investigate the effectiveness of using text messages to educate adolescent bisexual and gay men on HIV prevention. "It's a very interactive, intense dosing of education," Mustanski says. "We can really get away with sending them a good number of texts."

The texting program will send participants information on safe sexual practices and HIV prevention. The researchers will review the participants' sexual history after three months to measure the effectiveness of the messages.

Mustanski's team educated participants on possible privacy issues, and received IRB approval with "no major snags."

"Using this technology raises typical concerns about privacy and consent," he says. "We work with young people so that they understand the privacy of their phones, that they're the only ones who can see the messages, and what happens if other people see them. We've done formative work and focus groups this year, and we know they are the best ones at using their phones and knowing what's private and not private. The last thing we would want is for the parents of someone who is not out to see the messages and have a conflict.

"We deal with this every day as far as privacy with their sexual orientation," Mustanski says. "We have a waiver of parental consent because it might not be safe for the subjects to come out to their parents. We interview with the young person over the phone so they know the risks and benefits of the study. Similar studies haven't had problems with young people being hesitant."

Mustanski's studies have not yet expanded into smartphone apps. "Texting is still so ubiquitous," he says. "Apps are more limited to people who have smartphones. Though [smartphone] ownership is expanding very, very quickly, it doesn't yet meet the highest-need young people. If we're very successful with the text messages, then it could be used for smartphones."

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Speaker: Greater diversity needed in clinical trials

Conference raises need for pediatric studies

More subject diversity is needed in clinical trials to reduce the risk of adverse outcomes, according to the keynote speaker at the Clinical Trials in Georgia conference.

Valerie Montgomery Rice, MD, dean and executive vice president of the Morehouse School of Medicine, emphasized that more complete study results require diverse groups of research subjects.. By 2040, Montgomery Rice says, minorities will be the majority in the U.S. and will be the largest consumers of healthcare.

During a clinical trial, "there is a responsibility to ensure the safety and efficacy for all who will receive the drug, device or biologic," Montgomery Rice says. "But it doesn't happen nearly as often as it should. It's not intentional, but it is important to close this gap."

She identifies "the gap" as barriers keeping some populations from entering clinical trials, including:

- lack of access to medical care;
- mistrust of the study and its proposed goals;
- inconvenience — the study facility may not be in an accessible location;
- lack of information about the trial, or not even knowing the trial is going on;
- fear of participation.

And, according Montgomery Rice, principal investigators must work to bridge the gap and build community relationships in order to recruit a more diverse subject population.

The National Institutes of Health developed the Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research as part

of the NIH Revitalization Act of 1993, stating that NIH-funded studies must recruit women and minorities. The guidelines state that, in Phase III trials, "they must be included in numbers adequate to allow for valid analyses of differences in intervention effect," unless a compelling rationale has been established otherwise (for example, a drug being tested for conditions not seen in women).[1] However, Montgomery Rice says a gap still exists in privately funded studies.

Drugs and devices do not work the same on everyone — men and women, young and old, and different races and ethnicities all experience different outcomes. For example, a 2006 study in the *Journal of the American Medical Association* found that daily aspirin regimens have different protective effects for men and women — cutting the stroke risk in women but reducing heart attack risk for men.[2] And BiDil showed a benefit in African-American heart failure patients that was not seen in any other ethnic group.

"Despite [these] instances of specific health concerns disproportionately affecting varied populations, minority participation in clinical trials remains a challenge," Montgomery Rice says.

To increase diversity in research, the entire clinical landscape must be changed, she says. The clinical landscape includes:

- **Physicians:** They can "recruit PIs from a community network of physicians who care for a diverse population every day," she says.
- **Physician-scientists:** There should be more opportunities for physicians to become researchers.
- **Research staff:** "Create a team that is capable of engaging and retaining diverse populations," Montgomery Rice says.
- **Research subjects:** "Establish bilateral communication and commitment that aligns the needs of the community with the research agenda. This reduces barriers and creates opportunities," she says.

Recruiting principal investigators with strong community ties can also increase minority participation. Those who serve diverse populations build relationships with the subjects. "It is well known that by increasing the number of PIs who serve diverse populations, one can increase the recruitment of diverse populations," Montgomery Rice says.

"It is the responsibility of all who participate in research to recruit diverse subjects," she says.

Expanding pediatric clinical trials

Though federal mandates have ensured that more clinical research has included children, there is still much progress to be made, the chief researcher at Children's Healthcare of Atlanta (CHOA) said at the Clincal Research in Georgia conference.

"Children represent 25% of our population, yet fewer than 10% of registered clinical trials include children," says **Paul Spearman**, MD, who is also vice chair for research, Emory University Department of Pediatrics.

The Pediatric Research Equity Act of 2003 requires companies filing license applications for new drugs or devices to assess safety and effectiveness in children if the new drug will have a meaningful benefit. The Best Pharmaceuticals for Children Act of 2002 provides six-month patent extensions and other incentives for testing new medications in children. In February of this year, the Institutes of Medicine released its "Safe and Effective Medicines for Children" report, which analyzed the effects the two pieces of legislation had on clinical trials and that significant strides have been made, including 400 labeling changes.[3]

To promote more pediatric clinical trials, Spearman suggests the steps that his organizations have followed:

- striking master research agreements with contract research organizations and major pharma;
- recruiting a clinical/translational research leader;
- expanding outpatient research unit facilities; and
- establishing a Task Force for Clinical Research Processes between the CHOA and Emory University.

"Clinical trials in children is a national priority," Spearman says. "We all have a mandate to study new therapies in children."

Enhancing best practices

Speakers at the Clinical Research in Georgia conference also discussed the following:

— Creating informed consent materials that are more accessible and understandable to clinical trials subjects.

Studies have shown that only 86% of study subject read informed consent forms, says **Harry Cremisi**, MD, medical director at Morley Research Consortium and Opus Institutional Review Board,

and chairman of medical education Southern Piedmont Region at Novant Health, all in Charlotte, NC. Some issues to understanding the forms, he says, are patients feeling intimidated, low literacy, language barriers, participants not knowing what to ask, and patients feeling as though the trial is their only hope for treatment.

"Inadequate informed consent is not uncommon, and high-complexity trials pose special concerns," Cremisi says.

More guidelines are needed to ensure that informed consent is simple for patients to understand, he says. Possible guidelines include testing to ensure that participants have functional literacy and know enough about the trial to participate, having flexible informed consent templates, and being aware of consent and assent for certain subject populations.

"We are concerned for what patients are truly understanding," he says. "It's a very, very slippery slope."

— Making research sites more attractive to clinical trial sponsors.

A good foundation for trial sites includes appropriate staff to support research, appropriate accommodations with adequate space, and proper training for staff, says **Cheryl Lutz**, Southeast director of site management (Atlanta)of contract research firm Quintiles.

Other qualities for a successful site include good quality standing, experience and capability to do the trial, enrollment history, similar trials site conducted (screen failure, patient dropout rate, query rate, protocol deviations), turnaround time for critical documents, number of competing trials in enrollment at that site, and type of IRB.

— Expanding a research program.

The key to starting or expanding a good research program is to prioritize human subjects protection, comply with federal regulations, and contribute to medical science with quality data, says **Joan Dorin**, R.Ph., of director of clinical research at WellStar Research Institute in Atlanta. A good infrastructure includes a centralized research office for oversight of all research activities; research application process for all investigators; diligent regulatory compliance oversight; streamlined processes with legal and system compliance; and building the research organization from within.

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1. National Institutes of Health. Inclusion of Women and Minorities in Clinical Research. http://grants.nih.gov/grants/funding/women_min/outreach_qa.htm#1055
2. Berger JS, et al. Aspirin for the Primary Prevention of Cardiovascular Events in Men and Women. *JAMA*. 2006;295(3):306-313.
3. Institute of Medicine. Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. http://www.iom.edu/Reports/2012/Safe-and-Effective-Medicines-for-Children/Report-Brief.aspx ■

CNE/CME OBJECTIVES & INSTRUCTIONS

The CNE/CME objectives for IRB Advisor are to help physicians and nurses be able to:

- establish clinical trial programs using accepted ethical principles for human subject protection;
- apply the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this continuing education program and earn credit for this activity by following these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

COMING IN FUTURE MONTHS

Detailed minutes can enhance regulatory compliance

Avoid showdowns with PIs

Best practices in handling adverse events

Expanding your current research program

Bioethics training for IRB members

CNE/CME QUESTIONS

1. What is key to the whole genome sequence research policy, according to the Presidential Commission for the Study of Bioethical Issues (PCSBI)?
   A. recognizing the balance needed between the use of whole genome sequence technology, the benefits to society of this research, and the need for safety among individuals who contribute their genetic data to the research;
   B. making progress in genetic medical research;
   C. providing absolute privacy and confidentiality to individuals who donate tissue;
   D. none of the above

2. Which of the following is included in the PCSBI's recent report "Privacy and Progress in Whole Genome Sequencing"?
   A. Federal and state governments should ensure a consistent floor of privacy protections.
   B. Policies should prohibit whole genome sequencing without the consent of the individual from whom the sample came.
   C. Full informed consent should be obtained at the outset of diagnostic testing or research.
   D. all of the above

3. A research institution divides calls to a research protection program's complaint/questions line between those that are contacts and do not require follow-up action and those that are complaints that do require follow-up and/or an investigation. Which of the following examples would be a "contact" rather than a complaint?
   A. A study participant calls to say that he heard from a friend that the study coordinator was talking about his participation in the research to people outside of the research institution.
   B. Parents call to say their child was asked intrusive questions as part of a study, despite their declining to sign the informed consent form.
   C. A study participant calls to say that he has not received his compensation check and it's been a week since he completed the trial.
   D. A study coordinator calls to say the investigator skipped lab draws at visit five because of a scheduling conflict, but has not reported the change to the IRB.

4. According to Joel Hughes, PhD, which of the following is an advantage to using a medication compliance app in clinical research?
   A. Results can be reported to clinicians in real time.
   B. Study drop-out rates are lower.
   C. More patients will use smartphones.
   D. Both A & B

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