CLINICAL TRIALS
ADMINISTRATOR
An essential resource for managers of clinical trials

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Navigate the labyrinth of Medicare reimbursement for clinical trials

Experts discuss problems, solutions

If there is any doubt in the minds of clinical trials administrators and coordinators about the complexity of Medicare and insurer reimbursement in clinical trials, then they need look no further than what happened when the National Academy of Sciences convened a task force to address the subject five years ago: Its main proposals never were adopted.

"The medical leadership had a long series of meetings with the National Institutes of Health, and the issue was whether or not we could come to a joint agreeable position on Medicare and other insurer coverage of clinical trials," says **John Ludden**, MD, director of the MD/MBA program at Tufts University Medical Center in Boston. He was a member of the task force.

"This discussion had many aspects, but what stands out in my mind were a set of proposals that were never adopted by anybody," Ludden says. "The proposal was basically that Medicare should cover clinical trials, and care associated with clinical trials is really the issue, partly because it was absolutely — in my mind — unethical to both get patients into trials as subjects and also to require them to pay for their care."

This proposal's most contentious and difficult issue involved non-NIH-sponsored clinical trials, he notes.

While NIH-sponsored research proposals go through a rigorous scientific review process, the same may not be true for non-NIH trials, Ludden says.

"Would other trials in order to qualify for reimbursement go through a similarly rigorous process?" he asks. "We could not agree among ourselves about how that would work and who would pay for the vetting."

IRBs have become a little tighter in their scientific review in recent years but, nonetheless, there still are real questions about how one would administer this process and how a Medicare officer or officer of another insurer would know that clinical trial X had met the criteria, Ludden explains.

"The principle that Medicare pays for what it pays for whether or not it's part of a clinical trial still is the watch word," he says. "In other words, if XYZ is normally paid for by Medicare, it normally will be paid for and not disqualified because the patient is in a clinical trial."

However, assuring the proper Medicare reimbursement for medical services performed during the course of a clinical trial can be a little challenging.

"I think the evolving story in the area is the continuing concern about the appropriateness of billing Medicare for certain items in a clinical trial," says **Jan Murray**, a partner with Squire, Sanders & Dempsey LLP of Cleveland.

"There's concern about whether they're appropriately billing because it's very difficult for the system to determine whether the billing is appropriate or not," she says. "That's a real concern on the part of academic medical centers."

During President Clinton's administration, there was a national coverage decision to cover the routine costs of clinical trials, not including the use of investigational drugs and investigational devices that fall under Category A in which safety and efficacy have not been demonstrated, Murray notes.

"Category B devices are reimbursed, and the Food and Drug Administration determines which are Category A and Category B for the Centers of Medicare & Medicaid Services [CMS]," she reports. "Most will be Category B devices that have to go through a clinical trial because there's been a change, and the change doesn't affect the safety and efficacy of the device."

For example, there might be an electrical lead on a pacemaker that is being studied, Murray says.

Standard Medicare coverage

She offers these suggestions for improving Medicare billing compliance during clinical trials:

- **It must be a qualified clinical trial.** To be eligible for Medicare reimbursement the clinical trial must be qualified under national coverage determination (NCD), Murray says. "If a trial does not qualify, it may still qualify if it meets several criteria, which is complicated."

Clinical trials that solely use healthy volunteers are not covered, although if healthy volunteers are included as a control group in a trial studying patients with a disease, then the trial qualifies, she notes.

For example, one issue concerns what is routine care paid by Medicare, Murray says.

"Routine care is generally anything that is done that would ordinarily be covered under Medicare, so this has to be a trial that would ordinarily go for reimbursement and that is necessary for the

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Editorial Questions

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health and well being of patients," she explains. "And it has to be a service that is normally available to Medicare."

• **Clinical trial monitoring may be excluded.** Procedures done solely for monitoring purposes are excluded from Medicare reimbursement, Murray says.

"If you are doing a test to monitor complications, then it is eligible for Medicare reimbursement," she explains. "Or if the procedure is to treat or prevent complications, then it is eligible for Medicare reimbursement."

But items collected solely for data analysis and items that normally are provided free of charge by the hospital are not eligible for Medicare reimbursement, Murray adds.

"It has to be a qualified clinical trial and generally a clinical trial that provides services ordinarily covered under Medicare," she says. "It has to have a therapeutic intent."

• **Compliance can be a big issue for hospitals, particularly.** "It's not an easy rule to apply for hospitals," Murray says. "This is why there's a significant compliance issue out there that many hospitals are facing."

Each clinical trial has its own budget, and that budget combined with the protocol and clinical trial agreement will dictate what the sponsor or grant will finance, she says.

"Under Medicare, you can't submit a claim for services not covered, and, secondly, you can't submit a claim that someone else has paid because that's double billing," Murray explains. "So the two biggest concerns are telling what is covered and making sure that someone else has not paid for it."

One way to determine what's covered and what might constitute double billing is to look at the clinical trial agreement to see what is covered and what the budget is, she suggests.

"Look at the protocol to determine why something's being done and to be aware of what's communicated to the patient," Murray says. "The informed consent process is very important in this too because the informed consent has to include a statement that identifies to the patient what their financial identity is."

For example, if the informed consent document tells subjects that they or their insurer are not responsible for any costs in the clinical trial, then investigators and institutions cannot bill Medicare for the costs, she says.

"Those three documents: the clinical trial protocol, the clinical trial document, and the informed consent document are very important, and you should look at these for each trial," Murray says.

Other items to note are as follows:

— Which expenses include investigational items or services?

— Which tests are provided solely for data collection or analysis?

— Which sponsor or granting agency is paying for a service, so that an institution does not double bill that item?

Ideally, institutions would conduct this billing compliance process once a month, Murray says.

Another issue for academic medical centers is the flat rate per patient charge that may or may not include tests conducted during the course of a clinical trial, she notes.

"It's important for companies to identify what they're reimbursing academic medical centers for and to be aware that Medicare does pay for certain things, so perhaps they shouldn't pay for those," Murray says. "But they need to identify exactly what costs they're picking up to create a clean, nonfraudulent claim."

• **Clinical trials coordinators should know the routine costs of a trial.** "I think the important thing is for both parties to understand the routine costs of the trial and what the costs are that are being incurred that go specifically to the cost of the drug or investigational drug, device, or service," she says. "So if someone is collecting data to analyze the end points, but the data also will give them information about the complication they're concerned about that relates to safety issue, then it can be hard to distinguish what is reimbursed."

Clinical trials coordinators need to be aware of these issues and have a specific understanding of what is funded and what that funding means in terms of Medicare and other reimbursement, Murray adds.

This information should be communicated to the institution's legal staff or clinical research associates, depending on who is negotiating the budget with the academic medical center, she says.

• **Federal auditors are investigating some clinical trials.** Medicare concerns are becoming increasingly important and were mentioned in an OIG Workplan, Murray says.

"There's a major investigation that involves the use of investigational devices, and that one resulted in a number of hospitals settling for many millions of dollars," she notes. "So the feds are aware that this is a potential area of concern for clinical trials reimbursement and investigational device coverage, where there's a lot of room for

error and problems."

These recent investigations have heightened awareness in the research community, and some institutions have discovered that their main systems for billing Medicare do not accommodate research very well, Murray adds.

"They're all scrambling to come up with new ways to deal with this in-house, and that's a real challenge," she says.

The best bet for finding out more on Medicare reimbursement would be to contact legal counsel and consultants, including large accounting and financial auditing firms that could provide a billing analysis to determine whether an institution has been handling the Medicare billing properly, Murray says. ■

Clinical trials support office is a new trend

Institution plans call for increasing research

One way an institution can promote research and provide support to clinical trials coordinators and investigators is through the formation of a clinical trials support office.

Thomas Jefferson University of Philadelphia has recently formed a clinical trials support office as part of the university's strategic plan for expanding clinical trials, says **Roseann Talarico**, associate director of the clinical trials office at the university.

"What I'm working on is a mission and goals and part of it is supporting faculty members who are doing clinical research by providing a variety of administrative and clinical support services," she says.

One of the goals is to expedite the contractual process from the beginning when the principal investigator receives the protocol from the sponsor, says **Ronald Polizzi**, associate director of contracts at Thomas Jefferson University.

"It's done manually now," he says. "Our goal is to put a strong system in place that should speed up the process, make it simpler."

Ideally, once the support system is fully under way, principal investigators will have the information and assistance they need to feel comfortable pursuing new research contracts, Polizzi says.

"Principal investigators will be much more aggressive in reviewing contracts and protocols and say, 'I want to do this study,' instead of being hindered by roadblocks and delays," Polizzi says.

The process of forming the support office is about halfway developed, but its formation may provide a blueprint for administrators with other research institutions.

The blueprint includes these features:

— regulatory compliance training;
— business aspects of a clinical trial;
— documentation during a clinical trial process;
— role of the grants manager in clinical trials;
— flowchart for pre-award process;
— streamlined clinical trial process;
— pool of study coordinators;
— web site with internal and external links.

Polizzi and Talarico offer these ideas for what a clinical trials support office could do for an institution and its research staff:

• **Develop database of investigator interests:** "We're working on developing a database of principal investigators' interests and a database of the patient population by disease," Talarico says. "That information is not located in one central location."

The goal is to coordinate the information in such a way that as the university aggressively seeks to expand its research contracts it will be easy to match an investigator with a patient population, she says.

• **Form task force:** Thomas Jefferson University has a task force with four subcommittees, including a hospital, fiscal review, university, and Jefferson University physicians, Talarico says.

"The No. 1 issue is standardizing costs," she says.

The idea is to have an on-line description of the support office's services so fiscal managers can have the information readily available as they're preparing budgets, Talarico says.

"We're working closely with hospital representation on formulating a policy for fiscal review committee so we can delineate the expenses up front in a protocol and separate the standard of care vs. research expenses — so it's not a gray area after the fact," she explains.

• **Coordinate training/education:** When the Thomas Jefferson University clinical trials office is fully developed, one goal is to provide investigators, IRB members, and research staff with an idea of what training courses are available in every department, Talarico says.

"We'll have an on-line service so individual business managers can go in and see if key personnel have taken the training necessary to be on a clinical trial," she says. "We're working in collaboration

with the IRB to establish more educational programs for clinical faculty members and chairs."

• **Improve contract review process:** Principal investigators have expressed an interest in improving the contract review and negotiation process, Polizzi notes.

"We're trying to speed up the process," he says. "We want to have everything float smoothly from program to program with all processes in place, including the IRB, the clinical trials coordinator, the hospital — so they'll all have access to the same system."

To meet that goal, Polizzi and Talarico are meeting with hospital departments, learning each department's system, pricing, and management styles, Polizzi says. "We're trying to get everyone on the same page."

For example, contract language often is an issue as each department might use its own. "One answer is that we could coordinate between departments, he says.

This way, the informed consent language would match the contract language regarding patient identification and other items, Polizzi explains. "Sometimes the IRB or clinical trials coordinator is looking at it one way, and I'm looking at it another way, and that causes a delay, That's a problem where the departments need to communicate with each other, and if we had an on-line system, we could do that by logging on."

The way it works currently is that everything is on paper and everyone involved works in different buildings, he adds.

"We meet with coordinators monthly, and we're trying to break communication barriers so they can ask us what they need," Polizzi says.

The objective is to create a standardized contract template that could be used with industry sponsors, he notes.

"If we had a boilerplate to use with the same sponsor, all we'd have to do is change the statement of work because the master agreement would already be in place," Polizzi says. "We've already had six boilerplates with certain sponsors, and these will expedite contract negotiation."

Too often contract negotiations are hung up on the issues of publication and intellectual property, but with a boilerplate already negotiated, the hope is that these issues would already be resolved, he explains.

This would streamline the process, making it move along more quickly, and sponsors are receptive to the idea because it also saves them time and money, Polizzi adds.

• **Make the support office a one-stop shop:** "The goal is to support our faculty members so they can come to this clinical trials office for any aspect of the clinical trials process and we can coordinate all these processes for them," Talarico says.

"We also want to be able to make a type of business development office, another component where we can match up our investigators with industry," she adds. "We'd have a database of industry sponsors and principal investigators and hopefully that will increase our clinical trial activity."

The university already provides support for grant writing through its faculty development program, and Talarico's office is located with the office of research administration, so these support services work well together.

• **Create network for research professionals:** The Jefferson Clinical Research Forum was developed to create a network for research professionals and a mentoring system.

"We found there is a lack of coordinators," Talarico says. "Principal investigators could be watching two or three trials at one time and could do another two, but don't have the study coordinators or resources to hire them."

So the goal is to develop a pool of coordinators who could be loaned out to investigators, she says.

During interviews with principal investigators a recurring theme was they could take on another clinical trial if they had assistance, but the available coordinators were spread too thin, Talarico adds.

"If we could provide coordinators on a regular basis, this could increase their trial activity," she adds. "The issue is we're in a very competitive area with five major schools and a lot of pharmaceutical companies, and we find a lot of our turnover is to pharmaceutical companies."

Another goal is to provide more consistency in the training of coordinators, who typically come from a wide variety of backgrounds, including previous experience as clinical nurses, secretaries to investigators, etc., Polizzi notes.

"Say you have someone who became a nurse and decided to get into research," he notes. "That person may have a lot of knowledge about nursing, but not as much in research, so there's a lot of turnover and change among coordinators."

The institution's IRB provides a two-day coordinator session on the history of the IRB, and there are certification courses available, but more training is needed, Talarico says.

• **Provide pre-award proposal assistance:** One of the essential functions for the clinical trials

office will be the day-to-day activity for pre-award proposal assistance, Talarico says.

"We provide guidance and coordination of the Office of Research Administration and the Office of Scientific Affairs and Activities, including the IRB and human subjects protection," she reports. "We want to assist them with internal forms and the budget preparation process with the sponsor and creating a budget template."

The goal is to identify problem areas for the principal investigator in a timely fashion to facilitate the placement of trials, Talarico says.

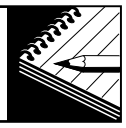
"We're looking at the feasibility of studies for our patient populations," she says. "We want to stay competitive, standardize costs, and create a central repository for all sponsors."

The support office staff will meet with principal investigators to find out what their relationships are with sponsors and to expand the repository, Talarico adds.

"We want to build a portfolio with specialties like therapeutic areas to match principal investigators and sponsors requirements in a timely fashion," she explains. "We would like to develop a marketing tool to develop outreach sessions to the community and pharmaceutical and medical device companies."

Once the clinical trials office is fully established, another goal is to have a toll-free number for the clinical trials, so members of the public can call to find out how they might become research subjects, Talarico adds. ■

GUEST COLUMN



State regulations are just as important as FDA rules

Lawyers say don't ignore state requirements

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Pharmaceutical companies conducting clinical trials in the United States tend to focus their regulatory attention solely on the requirements imposed by the FDA. This can be a mistake. Focusing on FDA regulations to the exclusion of state regulatory requirements may put the sponsor at risk. A large and increasing number of state requirements apply to clinical trials.

For example, while the FDA imposes the consent and, potentially, subject assent requirements, some states have adopted their own statutes regulating informed consent in clinical trials. For studies involving young children, some of the consent issues are fairly straightforward. In order for a child to be enrolled in the study, permission to participate must come from an adult — a parent or guardian. However, determining whether an adult has the authority to provide valid permission — which is not always a simple task — is governed by state law.

Determining applicable state law is also important when the study population involves older children. In many states, the age of consent is 18, but that is not the case universally. The age of consent is 16 in Kansas, Rhode Island, and South Carolina; but in Nebraska and Alabama, it is 19. Further complicating the issue is that the scope of the conduct to which a minor may consent differs among states. In addition, some states have emancipation laws, providing that an emancipated individual who has not yet reached the statutory age of consent is deemed to be an adult and thus capable of giving consent.

Participation by adults who lack the capacity to consent presents additional informed consent issues. As is the case for children, the determination of whether an adult has the capacity to consent is based largely on state law. And if the potential subject lacks the ability to consent for him or herself, state law determines who has the authority to authorize participation for the subject. Again, there is substantial variation among the states on this issue.

Another area where state laws loom large involves the issue of patient privacy. HIPAA contains requirements for protecting the confidentiality of patient identifiable medical information. In addition, many states have adopted their own privacy laws. If a state law is contrary to a provision in HIPAA, and the state law is more stringent, the state law prevails. If a state law and HIPAA are not contrary, a sponsor may have to comply with both laws. Many states have, in fact, adopted privacy laws that apply to clinical studies.

Genetic screening is another area where state law plays a significant role in clinical studies. Sponsors need to be certain that the informed consent form covers any genetic testing conducted on the subject's tissues in conjunction

with the pharmaceutical clinical trial. Many states that have laws regarding genetic testing require written consent for performing tests or releasing results, and some states specifically prescribe the elements of that consent. A consent form that meets FDA requirements may not satisfy state requirements. For example, Missouri requires patients be fully informed of the risks and benefits of releasing the information, and the identity of those to whom it will be released.

Moreover, sponsors need to be aware that genetic screening is an evolving area and state regulations are subject to change. As challenges are raised, state courts or legislatures may impose new requirements.

Sometimes, sponsors will want to test subject specimens for HIV. Sponsors and researchers should consider carefully the state requirements applicable to obtaining participants' HIV status in clinical research studies. Requesting and obtaining an HIV test result triggers a number of state laws. The vast majority of states require informed consent before an HIV test can be performed. Several states also strictly define what constitutes informed consent for an HIV test. For example, Colorado, Delaware, Iowa, Maryland, and New York require the ordering physician to inform the patient of the causes and symptoms of AIDS and provide information about the behavior that can lead to HIV infection. Once an HIV test has been administered, states require that a positive result be reported to the state health department. In addition, some states require the ordering physicians to provide face-to-face counseling about the meaning of the test. Physicians may also be required to help HIV-positive patients contact individuals who may be infected. Sponsors should not assume that they are exempt from these state laws just because the testing occurs during a clinical study.

Payments to investigators may present yet other state law issues. Although FDA requires that certain types of payments be disclosed, the agency does not restrict sponsor-investigator financial arrangements. Nor does it require disclosure of their arrangement to subjects. Nevertheless, payment could raise state law questions, including whether the subjects were adequately advised of any conflicts of interest. State law will decide the adequacy of disclosure.

Given that the focus has always been on the FDA, a natural question is whether these state law issues are of any practical concern to researchers. The answer is yes. Although many pharmaceutical studies are unlikely to implicate unique state requirements, this is not uniformly the case. Many studies have the potential to raise issues relating to conformance with state-established informed consent requirements. Furthermore, violations of state law can carry a variety of potential penalties. A plaintiff in a product liability suit also can use noncompliance with state informed consent or clinical study requirements.

In conducting pharmaceutical clinical trials in the United States, investigators need to be conscious of myriad regulatory requirements. Determining the applicable legal requirements and adhering to them would be much simpler if all that was needed was FDA compliance. While FDA regulations are, by far, the most important, they are certainly not the only regulatory requirements relating to research-related issues. The failure to be aware of state requirements can create legal problems. ■

Software Update

Clinical trials software offered free of charge

Software company has philanthropic goals

(Editor's note: In this issue, Clinical Trials Administrator *begins with this issue a periodic series on clinical trials software, looking at its use, potential, and availability. The software featured in this issue is eCTM, created by CyberMedica Foundation of Kennebunkport, ME.)*

The CyberMedica Foundation began in the late 1990s as a for-profit company created with venture capital money as a business that would create a framework for the drug discovery process from the beginning to end.

When that first effort fell victim to the dot com and technology stock market crash a few years ago, CyberMedica Foundation was formed by the original chief technology officer **Robert Stewart**, who purchased the intellectual property and assets of the for-profit entity to establish the nonprofit foundation, says Stewart, who now is executive director of CyberMedica Foundation.

"We're entirely privately funded and have a membership structure based on the size of an

organization and whether or not the organization is for profit or nonprofit/academic," he says.

Stewart's motivation in starting the foundation was his experience of losing a younger brother to a rare disease, which has convinced him of the need for faster research to produce faster cures. His brother died at age 9 of rhabdomyosarcoma, an aggressive cancer.

"He spent a lot of time at the National Institutes of Health in Bethesda, MD, and was on experimental drugs for his chemotherapy," Stewart recalls. "He was pronounced in remission, and then the cancer came back and took his life."

After doing his own market research, he was convinced there was no unified industry standard for the drug discovery process, and that the current process was inefficient and complex.

"As I came up to speed with industry, I gained an appreciation for how complex the cycle was and what influences are in that cycle," Stewart says. "It became my mission to develop this software, and when it became obvious the for-profit entity wasn't going to finish the job, that's when I took on the project personally, pouring every penny I have into getting it to this point."

Since his and the foundation's goal is to give the research industry a means for making the clinical trial process more efficient and faster, he decided to offer the software for free. This way, small institutions and clinical trials programs also may benefit from its technological assistance.

The software programs were made available to the public in July 2004, and there already are institutions using the system, which includes modules for funding and grants management, peer review publishing management, research and development collaboration, IRB management, as well as clinical trial management, is available for free use by any organization, whether it's a member or not. Each module can be integrated with the others, so an institution could use all of them in a way that would create data management efficiencies, Stewart reports.

"You could use just one module and not the others," he says. "However, I don't think you could get the same level of benefit as if you used all of the modules."

Another reason why Stewart decided to offer the software for free is because open-source technology permits each user to contribute toward improvements that will be built into modifications and revised versions of the software, he says.

"The application itself in five modules are going to change over the course of the next 20 years as technology changes," he explains. "This approach allows you to contribute your changes to the foundation's efforts, so updated modules will contain modifications you've made and contain modifications that other people have made, improving everybody's experience dramatically."

The best practices and approaches are integrated into the standards body, and each institution will not have to spend considerable time and resources in implementing and accommodating the software, Stewart adds. "The opportunities for efficiency here are astounding."

For example, it's possible that the integrated software modules will help an IRB's adverse event reporting taken into account the sensitivity of private data and the CFR Part 11 security requirements and propagate that information immediately, he notes.

"The integration of the modules will enable adverse event findings discovered during the clinical trial process to be reported directly into the IRB for immediate action," Stewart says. "This can have a tremendous acceleration benefit."

The system will require configuration, but a technology department could handle that, and if an office needed assistance, CyberMedica does have support staff available at a cost-recovery basis that includes a day rate for time and materials, Stewart says.

CyberMedica's system was created with peer review input. "A broad consortium of industry people sat side-by-side with software developers," Stewart says.

The clinical trials management software, called eCTM, can be used in this way:

• **Make certain hardware and software are adequate.** To use the software, an clinical trials office will need a server of Pentium class with 256 megabytes of RAM and enough hard drive space to hold data, Stewart explains.

The next step would be to go to the IBM link on the CyberMedica web site to download the latest version of Lotus Domino Server from IBM, he says.

• **Download eCTM.** A clinical trials coordinator could download just eCTM or all of the modules at www.CyberMedica.org, and they will automatically install in the appropriate directories, Stewart says. "Then you need to go to your web browser and connect your box to the network and then log in," he explains.

Documentation and training manuals also could be downloaded for free.

• **Ask questions:** Once everything is

downloaded, the next step is to write down questions and to try to identify gaps in what the software offers and what is needed, Stewart suggests.

"Once you define what those gaps are, then you would either talk to your own IT department to figure out if there is a Lotus Domino administrator on staff, who could help you make modifications, or you could contact the CyberMedica Foundation to create a statement of work from the notes," he says.

• **Input data:** Once the installation problems are resolved, it's time to key in the research data, Stewart says. "All the data recorded into the system is sacrosanct and can't be changed. You can create modifications to it, and these are only made by people who are appropriately authorized to do so."

As a clinical trials coordinator creates a protocol, the software system will create data collection forms for the trial, he adds. "If you go to the web site and click on 'demonstration' for an IRB module in particular, there is a demonstration video you can download and watch. There's a video demonstration of software being used for management of an IRB." ■

Genetics emerging new frontier for drug trials

Targeted therapy still in early stages

When the general public pictures genetic research, they think of new screening tests to detect rare diseases, or they think of cutting-edge gene therapy experiments that have the potential to completely reverse a previously fatal condition.

However, the real promise of genetic knowledge, say many experts, is in the potential to target drug therapy for common diseases, such as heart disease and cancer, that affect huge numbers of people.

"A lot of the efforts now are looking at common complex diseases, cancer, diabetes, or doing cardiac risk assessment," notes **Dawn Allain**, MS, CGC, president of the National Society of Genetic Counselors. "The idea is that if we can identify those individuals who are at increased risk for developing these diseases from a genetic perspective, then are there medical interventions, preventive treatments and lifestyle changes that we can do to prevent the onset of disease."

In the last few years, genetics has revolutionized research into cancer therapy as investigators have discovered links between certain genes and tumor grown and patient response to therapy.

For example, the drug Herceptin (trastuzumab) targets the overexpression of the human epidermal growth factor receptor 2 (HER2) that occurs in approximately 25% of women with breast cancer. Researchers working on the drug discovered that such over expression facilitated tumor metastases. For HER2-positive patients, combination treatment with Herceptin and paclitaxel can slow the cancers' progress.

In April, researchers at the National Cancer Institute discovered that lung cancer patients whose tumors featured a certain mutation in an epidermal growth factor receptor gene were more likely to show a favorable response to the drug gefitinib (Iressa).

Such discoveries may be just a drop in the bucket in terms of the potential for genetic information to direct therapy for different conditions, experts say.

One day, physicians may be able to determine which patients will do better from early initiation of drug therapy and which will benefit more from lifestyle alterations. Obviously, genetics can play a role in determining which patients will respond better to specific treatments. But, genetics may also point out which patients are more likely to suffer serious side effects from a particular drug, allowing doctors to use new drugs only in patients likely to benefit without undue risk.

"Heart disease, in my opinion, is not one disease, but many, many different diseases with similar characteristics," says **Janice Kurth**, MD, PhD, a geneticist and current vice president of life sciences for Visualize Inc., a software development company in San Diego. "The same is true of cancer. It is not one single disease, but many separate ones with separate causes. There are people who are very thin, who have very healthy lifestyles, who do everything right, and they still end up with heart disease. That is a patient who has a very large genetic component. There is also the couch potato, who weighs 300 pounds, doesn't exercise, and eats potato chips and watches TV all day and they don't get heart disease. Then, there is your average overweight, sedentary smoker who has the risk factors and gets it. We don't know whether they would get it without these risk factors or not."

Pinpointing risk factors

The ultimate goal for researchers is to discover which genetic risk factors cause disease and how that disease differs from the disease caused

primarily by environmental or lifestyle factors.

"When it comes to therapy, obviously, it would be really nice to know which groups of patients are going to respond to which therapies best. That really thin person that exercises and eats right but still has a cholesterol level of 250-260. They need early aggressive therapy. If we had a way to pick those people out, maybe we would start treating them in their teens or even childhood," Kurth says. "The next-door neighbor who really doesn't have the added risk, but needs to get out and run a bit and eat more vegetables, you might focus more on the lifestyle issues. The question is, can we get to a point where we can prevent — not only heart disease, but cancers and Alzheimer's disease — and also be able to treat patients early and treat them appropriately. That is the goal of what we would like to see in the long run."

Future: Targeted therapies

With all of the hype surrounding the completion of the mapping of the human genome in the early 1990s, many assumed that such targeted approaches were right around the corner. Reality has shown, however, that much more research will be needed before medical science can reach that point, she says.

In order to determine which gene mutations are linked to disease, and which are linked to drug response (pro or con), large-scale studies that collect genetic information from patients with these diseases are needed.

At this point, the funding mechanisms and research structures are not optimized to allow such research to proceed, Kurth contends.

Pharmaceutical companies, which sponsor most of the drug research in this country, are reluctant to fund studies that might place limits on the potential market for their compounds.

"The big pharmaceutical companies would really like to continue to develop big blockbuster drugs that will work in everyone," Kurth explains. "In designing clinical trials, they are really trying to show that [the particular compound] works. If they get a really good response in a smaller group of patients, then that is good, but they really don't want a label on it that is going to limit how it works."

Drug companies also are going to be very reluctant to fund studies that compare their drug with comparable drugs from other manufacturers to determine which patients might do better with their drug and which might do better with a competitor's — research which also is necessary if the science is going to advance as needed, she points out.

Not only is such research problematic for the companies from a market standpoint, but it is very expensive, Kurth notes. "Currently, we don't have the funding mechanisms in place that would support head-to-head research on the large scale that is necessary."

Sketchy subject compliance with treatment recommendations also complicates the ability of researchers to reliably determine which responses are due to genetic factors and which responses are the results of better or worse compliance with treatment, she continues.

"The largest contributor to the variance in how patients respond is compliance. Many people don't do what they are supposed to do, whether it is lifestyle or pharmacotherapy. And where we are looking for very, very subtle differences in response rates based on genetics, this may be a big obstacle," Kurth says. "I think, in many cases, we are going to find that it is not one single gene and one single thing we can point to, but a combination of things that cumulatively lead to variances in response. To be able to dissect the genetic component out from the rest is going to be very difficult."

At this point, many, many large-scale clinical studies are collecting DNA for genetic analysis, but research sponsors are largely taking a wait-and-see approach before pursuing actual genetic approach.

"They are collecting DNA samples from all of the patients in all of their trials. But to date, that is not being done actually as a part of the development process," Kurth notes. "In other words, they are storing that information. And their idea is really not let it interfere with the approval process now then later go back and do some work."

Herceptin was a rare example of a drug that actually used genetic information as a basis for drug development and as the key focus of their application for approval from the FDA, she says.

Kurth contends, however, that the future of drug development is in developing genetically targeted therapies for smaller populations. The big, blockbuster drugs have already been discovered. Yet, there is vast potential for discovering new therapies that work extremely well in certain subsets of patients.

"In theory, drug company A, B, C, or D would love to have something that is good for everybody. But I think we are well beyond that. The markets are already so fragmented, just because

there are so many competing compounds out there," she says. "We are fooling ourselves if we pretend it is not."

Second chance for 'bad' drugs?

The reluctance of companies to pursue genetic studies also means that many patients who could be helped by certain, high-risk drugs are not, Kurth notes.

Certain compounds have been pulled from the market or abandoned late in development that held great promise for a large number of patients, but also were found to carry the risk of devastating side effects for some patients.

"I have known of some drugs taken out of development somewhere in Phase 3 because some very, very rare events came up which were quite bad," Kurth says. "There have even been situations where drugs have been taken off the market because of really rare, but very serious, even fatal, adverse events. It is very difficult to pinpoint why, partly because they are so rare, why those things happened to those patients."

If researchers were able to pinpoint a factor influencing which patients were likely to suffer these rare adverse events, it would allow clinicians to prescribe the compounds for patients who badly needed the treatment and who did Snot risk the adverse side effects.

"If we could completely avoid treating those patients, the vast majority of patients could then safely take various compounds, which have been very helpful," she says.

In some ways, the positive coverage that genetic research received in the early 1990s when the Human Genome Project was completed has hurt the progress of gene research now, Kurth adds.

Patients and some medical professionals believed that gene therapies and targeted treatments were right around the corner when, realistically, that was not the case, Kurth says.

"We have a long ways to go before we can even get to that idealistic place," she says. "One of the ways the genetics community has probably erred in recent years is we somehow misled the public into believing we were going to be able to solve a bunch of complicated problems much quicker than we really can. All of these technologies have great promise. But because we are dealing with human lives, it takes a lot of work and a lot of time to do put it into practice ethically and properly. I think the public has expected more immediate rewards partly because of the hype that we in the community have put out there."

The science of genetics holds great promise for clinical research; however, Kurth emphasizes, just on a longer timetable than previously thought. "The potential is not gone, people I think are a disillusioned that we overpromised too early," she says. "We are not giving up and neither should our funding agencies and political support. ■

CE/CME objectives

The CE/CME objectives for *Clinical Trials Administrator* are to help physicians and nurses be able to:

- review pertinent regulatory mandates;
- develop practical clinical trial oversight strategies;
- review best practices shared by facilities that successfully conduct clinical trials. ■

CE/CME *questions*

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

9. When deciding which medical procedures conducted during a clinical trial may be billed to Medicare, which of the following is an important consideration?
A. The procedure must be done solely for monitoring purposes.
B. The procedure must have a therapeutic intent, such as monitoring for complications.
C. The procedure may be something that generally is provided free of charge by the hospital.
D. All of the above

10. In forming a clinical trials support office, which of the following is a good service to provide?
A. Regulatory compliance training
B. Business aspects of a clinical trial
C. Flowchart for pre-award process
D. All of the above

11. The age of consent in all states is age 18.
A. True
B. False

12. According to our article, which drug was developed using genetic information as its primary basis and information about genetic functioning was including in the application for the drug's approval with the FDA?
A. Iressa
B. Gefitinib
C. Herceptin
D. None of the above

Answers: 9-B; 10-D; 11-B; 12-C.