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Next-Generation Oral Anticoagulants

NOACs Are Game Changers But Offer Challenges for Anticoagulant Therapy

By Jaime Noguez, PhD

The recent introduction of several direct oral anticoagulants into clinical practice has not only transformed our approach to long-term anticoagulant therapy but has also added significant complexity. Although these new anticoagulants address many of the unmet needs of traditional therapies and may improve outcomes, they have their own limitations and we still have much to learn about them. The new drugs are called **n**on-vitamin K antagonist **o**ral **a**nti**c**oagulants (NOACs) because unlike warfarin they can reduce blood clotting without inhibiting the action of vitamin K.

A pharmacologic revolution is an exciting but trying time because of the lack of long-term clinical outcomes data and the arduous task of altering established practice routines. The introduction of new drugs can be particularly challenging if they lack companion diagnostic tests for monitoring their concentration or activity, as is the case with this new generation.

Clinicians and laboratory directors must adapt to the changing landscape of anticoagulant therapy by staying informed about new clinical evidence and potential diagnostic tools in the pipeline. This article provides a brief introduction to the NOACs, including their laboratory assessment, the challenges and opportunities associated with integrating them into clinical practice, and a perspective on the role of the laboratory in helping clinicians manage patients treated with these new agents.

Evolution of Anticoagulant Therapy

Anticoagulants have been used for more than 75 years for the prevention and treatment of thromboembolic diseases. Heparins (unfractionated heparin, low-molecular-weight heparins), fondaparinux, and vitamin K antagonists have been the mainstay of anticoagulant treatment and have proven to be effective and relatively safe. The limitations of these traditional anticoagulants include a slow onset of action and the need for frequent coagulation monitoring due to narrow therapeutic windows, variable pharmacologic effects, and multiple food and drug interactions. In addition, with the exception of warfarin, which can be given orally, the parenteral administration of these anticoagulant therapies makes them inconvenient for use outside of the hospital.

The shortcomings of the traditional anticoagulants prompted a target-based approach to drug discovery. This approach yielded a new class of anticoagulant drugs that selectively inhibit specific enzymes in the coagulation cascade without the mediation of antithrombin or carboxylation, which their predecessors relied on. In the early 2000s, a number of drugs that directly inhibit both free and clot-bound thrombin were brought to market, namely desirudin, lepirudin, argatroban, and bivalirudin (1). Their specificity for thrombin yielded a more predictable antithrombotic response, faster onset of action, and inhibition of thrombin-induced platelet activation and aggregation.

Although these direct thrombin inhibitors had several advantages over the traditional anticoagulants, they still required parenteral administration and all but one (desirudin) required routine monitoring to balance the risk of bleeding with clinical efficacy. This monitoring was particularly problematic because the drugs exhibited variable kinetics in assays used to monitor anticoagulant therapy (2).

A recently introduced class of direct anticoagulants exhibits the advantages of the previous genera-

Continued on page 2

Inside...

NOACs

Continued from page 1

tion along with many additional benefits, including an even more rapid onset of action, short half-life, oral administration, no food interactions, fewer drug interactions, and less dependence on liver metabolism (Table 1). Perhaps the most notable claim is that they can be prescribed at fixed doses without the need for adjustment or the inconvenience and cost of routine laboratory monitoring. These features are expected to provide the new NOACs with a therapeutic advantage, although much debate continues over the one-size-fits-all approach, given recent reports of bleeding events.

Table 1. Comparative Pharmacology of NOACs (21)

Drug Characteristic	**Dabigatran etexilate** (Pradaxa)	**Rivaroxaban** (Xarelto)	**Apixaban** (Eliquis)
Target	FIIa (thrombin)	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Bioavailability, %	6	>80	50
Hours to maximum concentration	1–3	2–4	3–4
Half-life (h)	14–17	5–9 healthy 9–13 elderly	8–15
Renal clearance, %	80	66	25

Non-Vitamin K Antagonist Oral Anticoagulants

The U.S. Food and Drug Administration (FDA) has approved three NOACs since 2010: dabigatran etexilate, rivaroxaban, and apixaban (3). All three are indicated for use in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation as well as treatment of and reduction in the risk of recurrence of deep venous thrombosis and pulmonary embolism. Only rivaroxaban and apixaban are indicated for the treatment and prophylaxis of venous thromboembolic events in patients undergoing elective hip or knee surgery. Clinical trials show that these new drugs are either non-inferior or superior to standard treatment regimens for the approved indications and additional studies are under way to further expand their uses. Several other NOACs in development may shift this new drug class to the frontline of anticoagulation therapy in the near future.

Dabigatran etexilate

Dabigatran etexilate (marketed by Boehringer Ingelheim Pharmaceuticals as Pradaxa) is the first FDA-approved oral direct thrombin (FIIa) inhibitor (Figure 1) (4). It is a prodrug that is rapidly transformed in the liver into its active compound, dabigatran, which reversibly binds to both free and clot-bound thrombin. Approximately 20% of dabigatran is conjugated by glucuronosyltransferases to the pharmacologically active acyl glucuronide conjugates, which have much shorter half-lives than the unconjugated form. Dabigatran is absorbed quickly and the oral bioavailability is very low (6–7%). Peak plasma levels are reached two hours after ingestion with a half-life of 14–17 hours in healthy individuals. Approximately 80% is eliminated predominantly unchanged by the kidneys, and the remainder is excreted in the bile after conjugation with glucuronic acid.

Dabigatran is a substrate of the P-glycoprotein efflux transporter, therefore co-administration with strong P-glycoprotein inhibitors or inducers can change dabigatran plasma concentrations.

Rivaroxaban

Rivaroxaban (marketed by Bayer as Xarelto) is the first FDA-approved direct oral anticoagulant against factor Xa (Figure 1) (5). It is selective, highly potent, and binds reversibly to the active site of free and clot-bound factor Xa as well as factor Xa in the prothrombinase complex. Rivaroxaban has >80% oral bioavailability with peak levels reached 2.5–4 hours postingestion. The half-life is 5–9 hours in healthy young people and 9–13 hours in the elderly. Higher doses should be taken with food to ensure optimal absorption. It is metabolized primarily in the liver by the cytochrome P450 enzymes and is also a substrate of P-glycoprotein transporters. Drugs that inhibit or induce only one of these metabolic pathways do not alter the plasma levels of rivaroxaban enough to require a change in dosage, but strong dual inhibitors or inducers can significantly change its bioavailability. Rivaroxaban has a dual route of elimination, with the majority being excreted by the kidneys (67%) and the remainder via feces.

Apixaban

Apixaban (marketed by Bristol-Meyers Squibb as Eliquis) is a highly selective and reversible inhibitor of free and clot-bound factor Xa as well as prothrombinase activity (Figure 1) (6). The oral bioavailability is >50%, with peak plasma levels reached at 3 hours and a half-life of 8–15 hours in healthy individuals. It is absorbed throughout the gastrointestinal tract, metabolized primarily in the liver, and has a dual mode of elimination by fecal (75%) and renal (25%) excretion. Apixaban is a substrate of both cytochrome P3A4 and P-glycoprotein, therefore coadministration with strong inducers or

inhibitors of them can make dose adjustments necessary because of changes in the bioavailability.

Reversing NOAC Effects

Bleeding is a complication of all anticoagulant therapies. Although NOAC use has received much support because of their safety profiles, bleeding complications still occur and unlike the conventional anticoagulants, there is no specific antidote to reverse their effects. The lack of antidotes is especially concerning because the clinical trials for these new drugs did not include high-risk populations, such as those of advanced age, with a history of bleeding, at extremes of weight, or with multiple comorbidities. Several antidotes for reversing the activity of the direct inhibitors are being developed with a few in clinical trials.

Despite the publication of approaches for managing serious bleeding complications (7,8), many clinicians remain wary of prescribing the NOACs because their institutions lack management protocols and experience in managing patients treated with them.

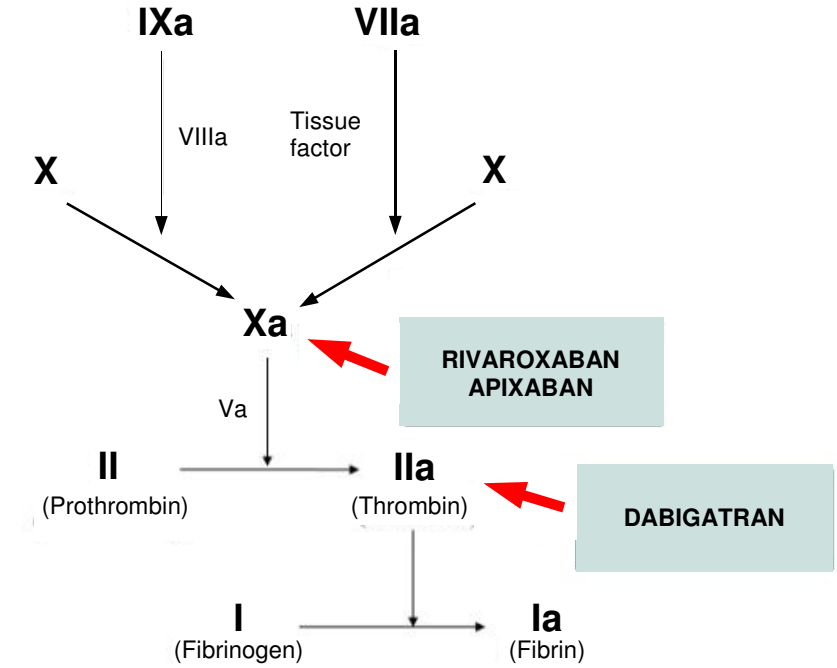

Figure 1. Schematic of Coagulation Cascade and Targets of Action for Novel Oral Anticoagulants

Current evidence-based guidelines recommend that bleeding management strategies be individualized according to the location and severity of the hemorrhage. In non-emergency situations, the next dose should be withheld and generic measures such as fluid replacement and hemodynamic support considered. However, more severe bleeding may require supportive measures such as oral administration of activated charcoal to decrease absorption of recently ingested drug (within the past two hours).

For removal post-absorption, hemodialysis can eliminate a substantial amount of dabigatran but is not as effective with rivaroxaban and apixaban because they are highly protein-bound (85–90%). The administration of coagulation factor concentrates such as prothrombin complex or activated prothrombin complex may help to manage severe bleeds by replacing clotting factors; however, the clinical data to support their use are limited.

When to Measure Anticoagulation

Although the NOACs were designed for use without the need for routine laboratory monitoring, there are a number of situations when being able to measure their anticoagulant effect would be useful, especially considering the lack of antidotes (Table 2). Laboratory assessment of NOACs might be useful for determining whether drug failure is the cause of an adverse event (thrombotic/hemorrhagic), checking compliance with the prescribed therapy, determining whether drug-drug interactions are affecting efficacy, perioperative patient management, suspected overdose, identifying drugs in unconscious or incoherent patients, checking patients with acute ischemic stroke prior to administration of thrombolytic therapy, and monitoring patients at risk for drug accumulation such as the elderly and patients at extremes of body weight, with impaired liver or renal function, and with suspected genetic polymorphisms.

Because the NOACs were designed to not require therapeutic monitoring, there are gaps in the evidence regarding the role of laboratory assessment for the surveillance and management of adverse events. Although based on limited test data, guidelines have been developed by professional organizations detailing how to evaluate patients on NOACs with coagulation tests (9,10). Readily available labo-

Table 2. Situations When Measuring Coagulation Intensity May Be Useful

Adverse events (thrombotic/hemorrhagic)
Checking compliance
Drug–drug interaction
Bridging anticoagulant therapies
Perioperative patient management
Suspected overdose
Drug identification
Populations at risk for drug accumulation
Elderly
Extremes in body weight
Patients with renal insufficiency
Patients with acute ischemic stroke prior to administration of thrombolytic therapy

ratory tests to gauge the intensity of anticoagulation would provide clinicians with valuable information to assist in making treatment decisions, but education of clinicians is necessary because incorrect test selection and interpretation can have dire consequences.

Laboratory Analysis of NOACs

Routine Coagulation Assays

Routine coagulations assays, such as prothrombin time (PT) and activated partial thromboplastin time (APTT) have limited to no utility in the context of the NOACs because they do not accurately measure the degree of anticoagulation (11,12). In general, these assays tend to be too insensitive or fail to demonstrate an appropriate linear dose response. Each drug has a unique effect on the clotting tests, which makes bleeding complications difficult to assess.

At high concentrations, all the NOACs prolong the PT and APTT, although rivaroxaban and apixaban affect the PT more than the APTT, and dabigatran affects the APTT more than the PT. The variable responsiveness of commercial reagent and analyzer combinations to the NOACs has made standardization across laboratories difficult (11,13). In addition, the NOACs cause spurious decreases in activity in PT- and APTT-based specific factor assays, false positives on lupus anticoagulant screening and confirmatory assays, incomplete correction in mixing studies, and overestimation of activated protein C ratio assay, which may lead to misclassification of patients with a FV Leiden mutation as normal.

The thrombin time (TT) assay is too sensitive to dabigatran to be useful. It shows a linear response only at subtherapeutic concentrations. At therapeutic levels the TT can exceed maximum measurement times. Even though the TT assay may not be useful at therapeutic drug levels, a normal TT can rule out a dabigatran anticoagulant effect. As direct factor Xa inhibitors, rivaroxaban and apixaban have no effect on the TT.

Dedicated Coagulation Assays

Given the limitations of the routine coagulation assays, modified or novel assays have been developed to measure the activity of these drugs, although no test is standardized or routinely available. These tests are also more expensive and, like all current laboratory tests, lack robust evidence to guide their use in managing patients treated with NOACs. The dilute thrombin time, ecarin clotting time, and ecarin chromogenic assays are the tests recommended for detecting dabigatran and have been investigated extensively (11).

The dilute thrombin time assay is similar to the conventional TT in that thrombin is added to plasma and conversion of fibrinogen to fibrin is measured, but it differs from the TT in that the patient's plasma is diluted to make the test adequately responsive. Diluting the patient's plasma to between 1:5 and 1:20, depending on the assay, provides a linear relationship between dabigatran concentration and activity. The Hemoclot Thrombin Inhibitor (HTI, Hyphen BioMed, France) is a commercially available assay that uses a 1:8 dilution of patient plasma and results in a linear dose response curve up to 1000 ng/mL (14).

Other assays use the enzyme ecarin, which is derived from the venom of the viper *Echis carinatus*. In the ecarin clotting time test, ecarin converts prothrombin into the thrombin precursor meizothrombin, which is inhibited by a direct thrombin inhibitor such as dabigatran. The residual meizothrombin that has not been bound by dabigatran converts fibrinogen to fibrin, which can be measured by a clotting time that is inversely proportional to the amount of drug in the sample.

The ecarin chromogenic assay is a modification of this test that uses a chromogenic substrate cleaved by meizothrombin. The chromogenic substrate generated can be measured spectrophotometrically and is inversely proportional to the dabigatran concentration. The plasma concentration of dabigatran can be measured indirectly by calibrating these functional assays with commercially available plasma standards and interpolating the patient's drug concentration from the clotting time.

Rivaroxaban and apixaban can be accurately measured by a chromogenic anti-factor Xa assay that uses a chromophore-linked substrate of factor Xa that generates a colorimetric change upon cleavage by factor Xa. This color change can be detected spectrophotometrically and is inversely proportional to the concentration of anticoagulant in the sample. The plasma concentration of rivaroxaban and apixaban can be measured indirectly by calibrating these functional assays with commercial standards that recently became available (15,16).

These dedicated assays are not yet FDA-approved or widely available, although they are being implemented in many clinical laboratories as laboratory-developed tests.

Mass Spectrometry

The concentration of NOACs in plasma can be measured directly via liquid chromatography-tandem mass spectrometry (LC-MS/MS), which is considered the gold standard. This technique offers greater selectivity and accuracy than activity-based coagulation assays and is less prone to interference. Several isotope dilution mass spectrometry methods were published recently after stable isotope analogs of all three NOACs became commercially available (17–19).

Some of these methods can quantify the plasma concentrations of all three drugs simultaneously (20).

Although LC-MS/MS is considered the superior technique for measuring the NOACs, it is not widely available and is often limited to specialized centers. Furthermore, even in clinical labs with access to it, it may not be not available 24 hours a day and 7 days a week, making this technique unsuitable for routine measurement.

Laboratory Role in NOAC Therapy

The significant variability among reagent and analyzer combinations for measuring the NOACs underscores the need for clinical laboratories to be aware of the sensitivity of their assays to each drug. Providing clinicians with this information and discussing the limitations of routine coagulation assays for measuring the NOACs are keys to reducing risk and increasing the safety of patients on these therapies. Appending an interpretive comment may help raise clinician awareness of the complex interactions that NOACs have with common coagulation tests.

Appropriate tests should be made available for the rapid assessment of anticoagulation intensity. These dedicated tests should be supplemented with support regarding test selection and result interpretation. Laboratory directors should keep informed of new tests in development and clinical data being published as the NOACs are integrated into clinical practice. As we continue to move into this new era of anticoagulant therapy, laboratories should assist in the development of institutional guidelines and testing algorithms to screen for these new agents and to provide clinicians with guidance about general best practices. Proactively addressing these concerns will increase patient safety and help clinicians feel comfortable prescribing these new agents.

Conclusion

Although in most cases routine laboratory testing is not required for the NOACs, there are still circumstances when assessment of the anticoagulant effect or plasma drug concentration may be useful. Laboratories should, therefore, be prepared to help clinicians make treatment decisions for patients on these new therapies. As the NOACs are integrated into clinical practice, laboratories need to be proactive by determining how their coagulation tests are affected by each drug, educating clinicians on the limitations of the current testing methods, ensuring that tests are available, and consulting about appropriate test selection and interpretation. Enhanced communication between clinicians and the laboratory is likely the best approach for navigating the rapidly changing landscape of anticoagulant therapy.

Learning Objectives

After completing this article, the reader will be able to describe how the non-vitamin K antagonist oral anticoagulants differ from traditional anticoagulants and be able to summarize the challenges associated with measuring the anticoagulant effects of these drugs.

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Krokodil

Desomorphine Returns As a Flesh-Eating Drug

By Heather Signorelli, DO, and Kamisha L. Johnson-Davis, PhD

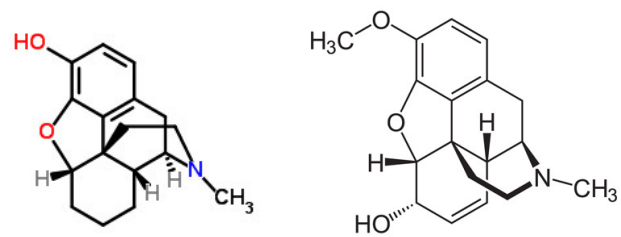
First synthesized in 1932 in the United States, desomorphine is an old drug that has recently re-emerged as a homemade injectable known as "krokodil." Krokodil first emerged in Siberia and the Russian Far East in 2003 because of the scarcity of heroin. Over the past few years its illicit use has spread and increased throughout Europe (1–3).

The name krokodil comes from the resemblance of an addict's green scaly skin to that of a crocodile. The drug's popularity probably stems from the ease of producing it from over-the-counter preparations of codeine and other toxic chemicals, which are thought to cause its devastating and unpredictable side effects.

Synthesis

The main ingredient in krokodil is a synthetic derivative of morphine, desomorphine (4,5a-epoxy-17-methylmorphinan-3-ol, dihydrodesoxymorphine, Figure 1) (2). Desomorphine was originally developed as a postoperative analgesic alternative to morphine with fewer side effects. It causes less nausea and significantly less respiratory depression than morphine, but is more addictive. Desomorphine has 8–15 times the analgesic potency of morphine, a faster onset of action, and a shorter half-life. The shorter half-life is thought to contribute to its addiction potential. Desomorphine was withdrawn from the market in 1952 and is now classified as a Schedule I drug in the U.S., not available even by prescription.

It can be manufactured easily at home by boiling codeine (Figure 1) and other readily accessible chemicals like paint thinner, gasoline, lighter fluid, hydrochloric acid, lead, iodine, and red phosphorus (3). The manufacturing process takes less than an hour and requires very little laboratory equipment to produce an orange-colored liquid with various toxic



Desomorphine Codeine

Figure 1. Chemical Structures

byproducts. The impurities in the drug are thought to cause its disturbing side effects.

Gas chromatography analyses of urine samples from persons consuming the street form of krokodil and samples from washouts from used syringes have identified varying amounts of synthetic analogues of desomorphine (trace to 75%) along with trace amounts of codeine and a number of other compounds (4). It is not known whether the other chemicals used for manufacturing influence the amount and composition of desomorphine. Given the wide variation in manufacturing practices, many krokodil cooks may not actually end up with desomorphine at all (2).

Clinical Effects

Krokodil is administered intravenously, subcutaneously, or orally (5). It functions as an opioid receptor agonist and can cause analgesia, euphoria, sedation, and respiratory depression. It is lipophilic and can penetrate the blood-brain barrier (6). Its fast onset of action (2–3 minutes) is similar to heroin's, but its duration is only about two hours. Tolerance can develop to the euphoric effects but not to the respiratory depressant effect (7). Because of the short half-life, users are in a constant process of acquiring the materials, manufacturing, and administering the drug in order to avoid withdrawal symptoms. Addicts can often neglect everything else, including their health.

The pharmacokinetics and toxic range of krokodil are not well-established. The serious toxic effects are unpredictable because of the wide variation in ingredients and manufacturing practices. The most common side effects are at the site of injection, with skin irritation causing a green-gray discoloration and scaly appearance. Destruction of the skin and soft tissue can occur along with substantial vascular damage, resulting in thrombophlebitis, peripheral ischemia, secondary infections, and even limb amputations (3). Severe multi-organ failure and other systemic symptoms related to iodine and heavy metals in the formulation have also been reported (5). Susceptibility to serious infections such as pneumonia, meningitis, and even sepsis are another major concern.

Death after a single use of krokodil is not uncommon. Chronic abusers rarely survive for more than one or two years, whereas heroin addicts often survive 20 years (3,5).

Reports on the toxicity of krokodil are primarily from media and self-reports on websites. Many wonder why a drug with such toxic side effects continues to gain traction in Europe and Russia. Many users claim they are unaware they are using krokodil and instead think they are using heroin.

Prevalence

Russia and Ukraine currently report the highest prevalence of krokodil, but its use appears to be growing in Europe (2,3,8). Russia has an estimated 100,000 to 250,000 krokodil users, and about 30,000 deaths per year associated with the drug. In Ukraine, there are an estimated 20,000 users. Between 2009 and 2011, there was a 23-fold increase in the amount of krokodil seized in Russia, and some believe it has become more popular than traditional opiate abuse. Codeine had been available over the counter in Russia, but because of krokodil's growing popularity, Russia began regulating the sale of codeine in 2012 to try to combat this problem.

There are numerous media reports of krokodil causing hospitalizations in the United States, but laboratory testing has confirmed only two cases (2,3,7,8,9). Some authors believe other drugs may be involved in the other alleged cases (3,10). More research detailing the extent of the problem and the geographic penetration is needed.

Testing

The best way to determine whether a patient has been exposed to krokodil is by measuring desomorphine analytically in serum/plasma or urine. Desomorphine can be detected for a few hours in the blood or one to three days in the urine after ingestion (5). It can be measured using liquid chromatography tandem mass spectrometry (LC-MS/MS) or gas chromatography-mass spectrometry. Currently, NMS Labs offers a desomorphine test in blood, serum, or plasma using LC-MS/MS.

Conclusion

Krokodil, once restricted to areas in Russia, has now invaded other areas of Europe and possibly the United States. Relatively easy and cheap to produce, it provides users with a high similar to that of heroin and is gaining popularity among drug users who can't afford or access heroin. Because krokodil can be produced at home by combining codeine with a number of toxic chemicals, the side effects are unpredictable and can be severe with high mortality. Mass spectrometry can confirm exposure in hospitalized patients with signs and symptoms of krokodil use. More research is needed to assess the true prevalence of krokodil use and the variations in its manufacture to better understand the clinical implications.

Learning Objectives

After completing this article, the reader will be able to list the chemicals used to synthesize the street drug krokodil and describe its adverse effects.

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Patient Access to Lab Results

Laboratories Should Be in Compliance With New Rules Giving Better Access

By Jennifer Collins, PhD

As of Oct. 6, clinical laboratories must be in compliance with new rules that allow patients to have direct access to their laboratory results. The new final rule, published on Feb. 3 with 240 days for laboratories to comply, amended regulations from the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. "These changes to the CLIA regulations and the HIPAA Privacy Rule provide individuals with a greater ability to access their health information, empowering them to take a more active role in managing their health and health care," according to the summary of the rule (1).

The new policy provides individuals or their personal representatives with the right to access test reports directly from laboratories subject to HIPAA and the right to authorize transmission of test reports to designated individuals or entities. Prior to the amendment, the Privacy Rule exempted CLIA-certified and CLIA-exempt laboratories from the provision that addressed the right of individuals to access their protected health information (PHI).

The change affects practices in more than two-thirds of the states—those where laws prohibited direct access to test results and those that had no laws defining who could directly access them. Only nine states previously allowed results to go directly to patients, and another seven states allowed patient access after provider approval. Patients can continue to request laboratory test reports from their physicians and other healthcare providers, but these changes give them additional options to access the information while retaining privacy protections.

Background

By way of background, the "CLIA Program and HIPPA Privacy Rule; Patients' Access to Test Reports" was originally proposed for public comment in 2011 (1). The final rule was issued jointly by three agencies within the Department of Health and Human Services (DHHS): the Centers for Medicare and Medicaid Services (CMS), Centers for Disease Control and Prevention (CDC), and Office for Civil Rights.

The CLIA regulations in place prior to the rule change limited the entities to whom laboratory test results could be disclosed to three categories: the in-

dividual authorized under state law to order or receive test results, the individual responsible for using the test results in the context of treatment, and the laboratory ordering the test. This regulatory limitation was viewed by some stakeholders as a barrier to the exchange of health information and as preventing patients from taking a more active role in their healthcare (1). The final rule permits laboratories to provide copies of completed test reports directly to a patient, the patient's personal representative, or a person designated by the patient, provided that the laboratory can authenticate the requester (2).

Privacy Rule

Although the HIPAA Privacy Rule generally provided individuals with the right to inspect and obtain a copy of their PHI, it included a set of exceptions related to CLIA. The exceptions covered test reports and other PHI only at CLIA and CLIA-exempt laboratories and did not apply to other entities such as hospitals or treating physicians. The rule change guarantees that the laboratories have the same obligations as other covered healthcare providers with respect to patient access to their PHI (3).

The changes apparently originated from the Health Information Policy Committee, a federal advisory committee comprised of representatives from major healthcare constituencies. This committee is tasked with making recommendations on developing a national health information infrastructure that is key to the DHHS and CMS goal of more widespread adoption of electronic health records. Facilitating access to one's personal health records is aimed at eliminating a barrier to sharing health information, which is perceived as an important step in motivating patients to take a more active role in their healthcare decisions.

Based on the recommendations, CLIA staff within CMS worked with the Office of the National Coordinator for Health Information Technology, CDC, and Office for Civil Rights to craft the proposed changes.

Public Comments

More than 160 public comments from a broad array of interested parties were submitted after the proposed rule was published in September 2011. Each comment was addressed and the final rule included minor clarifications and conforming changes. Laboratory organizations, including the American Association for Clinical Chemistry, College of American Pathologists, and American Clinical Laboratory Association, generally supported the rule, while expressing concerns related to the verification of patient identity, the value of laboratory results outside the context of physician consultation, and the length of time provided for compliance (4–6).

In response to concerns regarding patient verification, DHHS indicated that because the HIPAA verification requirement remains in place, a laboratory is not obligated to provide access to PHI if the requesting individual cannot be authenticated.

With regard to the timeframe for compliance, many larger laboratories and healthcare systems have already developed electronic solutions for providing patients access to healthcare information, but smaller entities may have to develop new protocols and procedures.

Some providers and laboratories expressed concerns regarding the release of reports for more "sensitive" testing, such as genetic, cancer, and mental health screening. However, the department declined to add any exemptions to the HIPAA Privacy Rule, which currently includes a very limited exception to the individual's right to access based on a determination by a licensed healthcare professional that the access requested is "reasonably likely to endanger the life or physical safety of the individual or another person (3)."

Practical Aspects of Implementation

The rule does not specify how patients must request or providers must respond to requests for lab reports, instead permitting flexibility in how systems are set up. Large reference laboratories such as Quest and LabCorp have already established patient portals (MyQuest by Care360, LabCorp Beacon) (7,8). Laboratories that interact more directly with patients may permit requests for results when individuals are at the laboratory for specimen collection. A wide range of processes for requesting information and verifying patient identify are likely to be used across the healthcare system.

Applicability

The final rule applies to all laboratory test results subject to CLIA regulations, which basically means tests performed "for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings (9)." The CLIA regulations do not apply to employers or other entities performing substance abuse testing for the purpose of employment screening in which test results are used only to determine compliance with conditions of employment. Results used in counseling or other forms of treatment for substance abuse disorders are covered by CLIA and are therefore subject to the rule.

Learning Objectives

After completing this article, the reader will be able to summarize the revisions to the CLIA program and HIPAA Privacy Rule that permit patient access to their laboratory test results.

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