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Unlocking the Potential of Continuous Glucose Monitoring: A New Guideline Supports the Development of Continuous Glucose Monitoring Devices

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Abstract

Continuous glucose monitoring (CGM) is a new technology that allows patients to measure glucose levels continuously over several days. It has several advantages over traditional glucose meters in that it does not involve repeated finger sticks and can measure trends and track changes in glucose levels over time. The Clinical and Laboratory Standards Institute, working with the Diabetes Technology Society, published Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline, which provides recommendations for methods for determining analytical and clinical metrics of CGMs. The document provides guidance on how CGM data should be presented, compared between devices, and compared between measurement technologies. The document serves as a roadmap for the testing of CGM devices and will ultimately advance the potential of this exciting technology. Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline represents the consensus view on preparing and presenting CGM data.

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Continuous glucose monitoring (CGM) devices have emerged as promising technologies in the field of diabetes treatment. For patients with diabetes, the use of self-management of blood glucose (SMBG) devices, or glucose meters, have improved overall health and reduced the long-term complications of the disease. Self-management of blood glucose devices are typically used to measure glucose levels one to four times per day in order to manage medication dosages. Although the currently available devices are easier to use now than in the past, some patients still do not to adhere to their doctors' prescribed testing regimen. Poor adherence is partly due to the inconvenience of testing, the cost of supplies, and the pain of repeated finger sticks.

Continuous glucose monitoring involves measuring glucose levels in the interstitial fluid in the skin. Continuous glucose monitoring devices can be worn for several days and can display not only glucose results, but also the direction of glucose change (up, down, or stable) as well as the magnitude of change (amount of glucose change per minute). Continuous glucose monitors

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Abbreviations: (CGM) continuous glucose monitoring, (CLSI) Clinical and Laboratory Standards Institute, (FDA) Food and Drug Administration, (POCT05-A) Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline, (SMBG) self-management of blood glucose

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thus offer the potential to predict hypoglycemic events before they occur, monitor for glucose variations that may not be detectable with SMBG monitoring only a few times a day, and present a comprehensive pattern of glucose values around the clock for determining therapy adjustments.[1]

In order to build upon the advantages of CGM, advance the technology, and enable patients to benefit from technological advances, it is worthwhile to take steps to achieve consensus on the best way to present and compare data on CGM devices. Ultimately, such guidance will enable new and better CGM devices to be developed and brought to market.

To that end, the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS), working with the Diabetes Technology Society, has released a new guideline, *Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline* (POCT05-A), which provides recommendations for determining analytical and clinical metrics of continuous interstitial fluid glucose monitors.

The process of development for POCT05-A began in 2004 at the annual Diabetes Technology Society meeting, where Steve Gutman, M.D., M.B.A., former Director of the U.S. Food and Drug Administration's (FDA's) Office of *In Vitro* Devices, initiated a project proposal. Over the following year, an international panel was organized to develop the CGM project. In November 2005, the Diabetes Technology Society, with the support of the FDA, created the scope of work for the project. In 2006, the CLSI became part of the process, and at the end of 2007, the proposed-level document was completed. In order to achieve the approved-level document, the committee wanted to make sure every voice was heard and every comment was addressed. This type of dedication to consensus and excellence is characteristic of CLSI volunteer committees and the standards and guidelines they produce.

Arleen Pinkos, M.T., ASCP, FDA Center for Devices/ Radiological Health, an advisor to the committee that developed the document, describes the experience saying,

> The document provides an excellent framework for product developers, manufacturers, and FDA. Using the consensus process to agree on the basic concepts and elements that impact the safety and effectiveness of continuous glucose monitors creates a foundation of understanding among stakeholders. The subcommittee brought together experts with various perspectives and allowed them to share their knowledge of and experiences with CGM sensors. These products are unique in terms of both the volume and types of information they provide, and this made it important to agree on the metrics for characterizing and evaluating them. Everyone working on this document was passionate about moving this technology forward, which will undoubtedly improve patient care.[2]

A Guideline to Accelerate Development

The new POCT05-A document provides guidance for health care professionals, *in vitro* diagnostic and medical device manufacturers, and regulatory agencies on how CGM data should be (1) presented, (2) compared between devices, and (3) compared between measurement technologies. Terminology is defined for measuring interstitial fluid glucose levels and comparing them to blood glucose levels. The degree of agreement for acceptable technical performance is defined to assess method comparability.[1] In addition, the document defines multiple aspects of analyzing CGM performance data, including point accuracy, trend accuracy, sensitivity and specificity, device stability due to changes in sensitivity over time, calibration, lag time, trueness of measurement, and device traceability.

David Klonoff, M.D., FACP, Diabetes Technology Society and Chair of the CLSI subcommittee in charge of developing the POCT05-A guideline, says,

> A manufacturer who is developing a CGM must test many aspects of performance, including conditions of rising and falling glucose levels, extreme values at the high and low end of the physiologic range, and in various location settings. Many data points are collected. Given the multitude of choices, there are different ways of defining metrics. If a manufacturer wants complete the development process quickly, then it needs to know what types of studies and what levels of performance are appropriate. Therefore, appropriate clinical trials can be built into the testing process to maximize device performance within a fixed budget of time and money. This guideline provides a roadmap to manufacturers about what clinical studies to perform and what data to submit in order to bring a product to FDA. For FDA, this guideline can be used as a tool to assess performance of devices …. We hope this document will assist manufacturers to bring more CGM products and better CGM products to market. When various new and improved CGM

products appear on the market, they increase the potential for patients to receive better medical care. In addition, with respect to new and improved CGM devices, these products could bring us one step closer to creating an artificial pancreas.[3]

The artificial pancreas is a device in development that could be worn externally and would be composed of a continuous glucose monitor, an insulin pump, and a computer chip that allows the two devices to "talk" to each other and calculate how much insulin a patient needs at any given time. This type of exciting advance in the treatment and management of diabetes is part of the bright future of CGM technology.

"This field is still evolving, and sensors are getting better and better. For this reason, the POCT05-A document is flexible, rather than prescriptive. This allows the metrics to apply not only to current sensor technologies, but also to future iterations of CGMs," adds Pinkos.[2]

Partnering with the Food and Drug Administration

This new guideline is aimed at providing a resource for manufacturers so they can comply with regulations. Pinkos explains, "The CGM guideline creates a level of expectation for both manufacturers and FDA, i.e., what information should be included in a marketing application to FDA and what information FDA needs to assess the scientific and clinical aspects of the device. Guidelines, such as POCT05-A, are voluntary and are not binding to either FDA or industry, but they are a valuable tool. We find that when they are followed, the time required for us to make our decisions is decreased."[2]

Barry H. Ginsberg, M.D., Ph.D., Diabetes Technology Consultants, who volunteered on the committee that developed the document, adds, "The new CLSI guideline not only provides specifications for FDA approval of CGM devices, users of the device will understand that it meets these quality standards."[4]

The approved-level version of the document, which replaces the proposed-level document released last March, accurately reflects the consensus of understanding of certain aspects of this changing field. Klonoff explains,

In the proposed-level document, the subcommittee felt that the metrics for sensitivity and specificity of CGM did not have a clear consensus with respect to dangerously high and dangerously low cutoffs at these levels. On the topic of alarm performance, it was premature to achieve consensus. It was deferred to a future edition of this guideline, and it was suggested that the diabetes technology community discuss, publish, and read reports and perhaps will reach consensus after this review. The next time the committee meets for the second version of the guideline, the subcommittee will determine if metrics can be defined for alarm performance.[3]

The CLSI prides itself on the integrity, openness, and transparency of its unique consensus process in the development of standards and guidelines in the health care and medical testing communities. The resources it provides represent the collective view of members of the medical community, industry, government, and academic institutions. The CLSI is a volunteer-driven, membership-supported nonprofit organization that, through this consensus process, provides reliable, practical, and achievable products to support an effective quality system.

For more information on CLSI documents and resources, visit *www.clsi.org*.

Reference:

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