WHITE PAPER

Use of “Limited Lead” ECG Devices

ECG Devices with Varying Leads: Utility and Use-Cases for Limited-Lead ECG Devices

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CLARIO.

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For most of the past 60 years, electrocardiographic recordings have fit largely into two categories: 10-second 12-lead ECGs, and continuous single channel (holter) recordings. With the rapid advancements in computer technology and digital storage, both 12-lead ECGs and holters moved from analog to digital recording and storage, and digital holters advanced from collecting a single channel to being capable of collecting a continuous 12-lead ECG recording for 24 hours or even longer. The basic concepts have remained relatively unchanged, however: 12-lead ECGs record 10 seconds of all 12 standard leads, and holters provide for longer duration recordings.

During the past few decades, there have been a small number of newer technologies for recording ECGs of varying durations. “Event recorders” have been in use since the 1980s; these are devices that either record a short strip when a patient applies the device during a period of symptoms, or that are worn continuously, and record a strip either when the patient activates it during symptoms, or if an internal algorithm detects a rhythm or conduction disturbance. These devices are very useful when patients have intermittent symptoms that may be related to rhythm disturbances, but which are infrequent enough that they aren’t likely to be detected even with a 24 hour holter monitor, let alone a 10 second ECG recorded while in the doctor’s office.

TECHNOLOGY ENABLING DATA COLLECTION OUTSIDE THE MEDICAL FACILITY

During the past decade, as microelectronics have continued to advance, several new technologies have been developed that enable collection of electrocardiographic recordings in new ways, often outside of the setting of a medical facility. First, there are a number of devices that utilize either several standard ECG electrodes or a patch-like electrode worn on the chest, and record one or two leads continuously for up to several weeks. These can capture either patient activated recordings, or recordings when the built-in algorithm detects an abnormal rhythm or conduction abnormality. Some devices simply store the data for subsequent retrieval, while other devices use a cellular device to transmit event recordings in real time to a monitoring station. Finally, there are also implantable devices that can monitor the cardiac rhythm continuously, capture and store recordings of arrhythmia events, and that can have data downloaded by a physician.

PERSONAL DEVICES WITH CLINICAL UTILITY

More recently, with the advent of “smart watches” and activity monitoring wristbands (such as the FitBit device), a number of new methods for recording electrocardiograms have been developed. One of the first was the AliveCor KardiaMobile device. The first iteration of this was a small iPhone case that included two metal electrodes and a downloadable iPhone app. This could be used to collect a single lead recording (analogous to standard lead I) by touching a finger on the right hand to one electrode, and a finger on the left hand to the other. While Lead I is not ideal for many purposes, it is very useful for detection of rhythm disturbances, particular detection of atrial fibrillation.

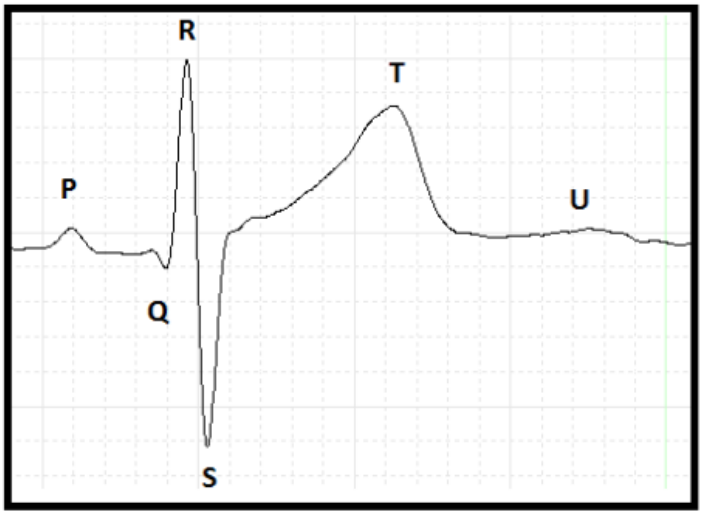
Recently, a new version of the KardiaMobile device has been released, this one including a third electrode on the bottom of the device, which can be placed on the left leg (at the knee or ankle), while the two electrodes on the top of the device are contacted by fingers of the right and left hand. This allows collection of standard leads I and II, from which lead III and the remainder of the “limb leads” may be mathematically derived. In other words, the 6-lead device (KardiaMobile 6L) allows an individual to collect a 6 lead ECG (for about 30 seconds) that is essentially identical to the 6 limb leads of the standard 12-lead ECG!

A BRIEF HISTORY OF ECG MEASUREMENTS

The first ECGs were recorded during the late 19th century, and Willem Einthoven is credited with recognizing what we now think of as the components of the ECG. Einthoven described the pattern of waves which represent atrial and ventricular events, and ultimately created the

naming convention which is still used today. A typical ECG complex, as shown in Figure 1, contains a P wave (representing electrical activation of the atria), a QRS complex (representing electrical activation of the ventricles), a T wave (electrical repolarization of the ventricles), and a small U wave (whose genesis remains a matter of debate).

Figure 1 **Single ECG Complex Showing P, Q, R, S, T, and U Waves**

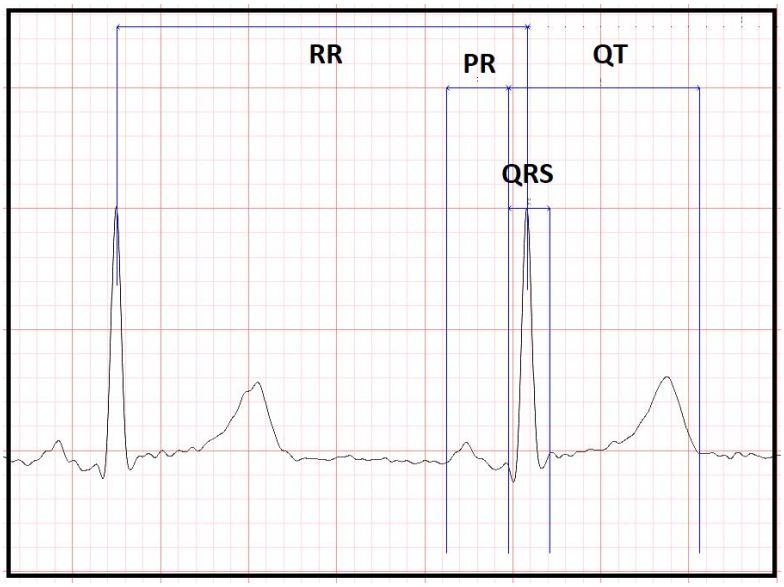


Based on these features on the ECG, a series of measurements can be performed. First, the RR interval, is the interval between successive QRS complexes, and is inversely related to the heart rate. For each ECG complex, we measure the PR interval (also known as the PQ interval), the QRS duration, and the QT interval. Each of these interval duration measurements (IDMs) has a physiologic analog: the PR interval represents the time it takes for the initiation of atrial activation, conduction through the atria, and conduction through the AV node and His Purkinje System. The QRS complex begins with the initiation of depolarization of the ventricles, and the QRS duration is the total duration of electrical activation of all ventricular tissue. Finally, the QT interval (which also includes the QRS duration) is the total duration from the first electrical activation of the ventricles until the end of ventricular repolarization, which sets up the cardiac tissue for the next electrical cycle. These measurements are illustrated in Figure 2.

Since the QT interval varies inversely with heart rate, we traditionally use the "corrected" QT interval, or QTc interval, for analysis. There are a number of different methods for correcting the

QT interval for heart rate; the most commonly used are the Bazett correction (QTcB = QT / (RR) $^{1/2}$) and the Fridericia correction (QTcF = QT / (RR) $^{1/3}$).

Figure 2 Single QRS with Calipers



All of the IDMs are important to consider during drug development. Drugs may increase or decrease the heart rate, which depending on the magnitude and the particular patient population may have significant consequences. Drugs which lengthen the PR interval may produce heart block and symptomatic bradycardia or syncope. Drugs which prolong the QRS duration may predispose patients with structural heart disease to an increased risk of sudden cardiac death. The QTc interval, however, is by far the ECG measurement which generates the most interest during drug development. In fact, detection of drug induced QT prolongation is probably the single most important aspect of cardiac safety during the drug development process. It's important to note that all of these measurements can be performed on a single ECG lead, most commonly lead II.

Einthoven and other electrocardiographers of the late 19th and early 20th century recorded electrocardiograms using electrodes placed on the limbs only, and these recordings include only

leads I, II, and III. These allowed only a look into a limited region of the heart. In 1934, Dr. Frank Wilson developed the concept of the 'central terminal'. By connecting the three limb electrodes, a central negative lead reflecting a 'ground' or reference terminal was created. By connecting an electrode to any point on the skin and measuring the voltage difference between this "exploring electrode" and the central terminal, one can measure the voltage difference (compared between the exploring electrode and the mathematically derived "Wilson central terminal") at any point on the body surface. This is referred to as a "unipolar lead", though in fact it is a bipolar lead measuring the voltage difference between the exploring electrode and the central terminal. In 1938, the American Heart Association and the Cardiac Society of Great Britain published their recommendation for recording the exploring lead from six sites named V1 through V6 across the precordium. As a result, the precordial (chest) leads came into common use. Finally, in 1942, Dr Emanuel Goldberger added three unipolar frontal leads, the 3 "augmented" limb leads, bringing electrocardiography up to 12 leads – which are still in use today.

The introduction of the precordial or "chest" leads (leads V1-V6) was a huge advance in electrocardiography. The 3 standard limb leads allow one to accurately assess the cardiac rhythm (or rhythm abnormalities) and cardiac conduction (or conduction abnormalities), but do not really record very good data from large parts of the heart – including much of the left ventricle, the largest and most important of the cardiac chambers. Prior to the development of the precordial leads, some conduction abnormalities (such as right bundle branch block and left bundle branch block) were not well characterized, and myocardial ischemia and myocardial infarctions involving the anteroseptal and anterior walls were often undetected. The availability of 12-lead ECGs dramatically improved our ability to detect and monitor ischemia and MIs, and certainly contributed to the development of the treatments for coronary ischemia and MI that have revolutionized modern cardiac care.

CURRENT ECG COLLECTION METHODOLOGIES – THEIR PLACE IN CLINICAL TRIALS

It's important to remember that new medical devices are generally developed for use in clinical medicine, as that is a far larger market than the clinical trial space…. with potential for far larger financial return. Furthermore, in clinical medicine, data are collected at the request ("prescription") of an individual patient's physician, and are reported only to the individual patient's physician (and the patient). In contrast, clinical trials employ very different

paradigms. Some data are collected to allow point of care decisions about inclusion/exclusion criteria, dosing decisions, or detection and management of emergent clinical issues during the trial. Data may also be collected for analysis at the protocol and compound program level, allowing evaluation of the safety and efficacy of the compound at a broad level, allowing go/no go decisions and enabling regulatory submissions. Certain types of data may be suitable for one of these uses exclusively, while other data may be useful both for point of care decisions as well as program-wide analysis. Some types of ECG data may have very limited use, while other types of data may allow a far broader assessment of cardiac safety.

One simple rule of thumb is that the fewer the leads, the fewer the uses of the ECG data. Another caveat is that the longer the recording, the greater the probability of detecting fleeting events. A single lead recording may be useful for detecting rhythm and conduction abnormalities, but may be completely useless for detecting myocardial ischemia or congenital repolarization syndromes and certain cardiomyopathies. In the following few paragraphs, the appropriate uses of each technology will be summarized.

Single lead ECG recordings (event / loop recorders, patches, wristband and watch systems, single lead holters)

These devices record a single ECG lead, often lead I. They are useful for monitoring heart rate, and for detecting certain rhythm and conduction disturbances. Specifically, they are useful for detecting atrial fibrillation/atrial flutter, other supraventricular tachycardias, ventricular tachycardias, bradyarrhythmias and pauses, and AV conduction block. They are also very useful for monitoring the functionality of implanted pacemakers, and are useful for routine trans-telephonic monitoring (TTM) after arrhythmia interventions (medications, cardioversion, and catheter ablation). They may be limited by the specific lead recorded – some leads are less able to show atrial activity, and may only allow assessment of the rate and regularity of ventricular rhythm. Depending on the duration of recording and their use (continuous vs patient or algorithm triggered recording), they may be useful for monitoring different types of events. Single lead ECG recordings tend to be very limited for detecting ischemic events, electrolyte abnormalities, or chamber enlargement. Patch devices may be worn for 7-14 days, and are very useful for quantifying heart rate changes over time as well as for detecting infrequent rhythm or conduction disturbances that may not be captured on a single 24-hour holter recording.

Limited lead ECG recordings (2 or 3 lead event recorders, holters, or patches, and 6-lead AliveCor KardiaMobile 6L)

These devices have more than one lead, which may be extremely helpful in more accurately identifying rhythm or conduction disturbances. Atrial activity (P waves) may not be visualized well in single lead recordings (especially lead I), and may be far more easily identified in 2 to 6 lead recordings. The AliveCor 6-lead device is ideal for monitoring for recurrence of atrial fibrillation after addition of a new antiarrhythmic medication or after a cardioversion or ablation procedure, as detection of atrial activity is far superior to single lead ECG recordings. The 6-lead recording of all 6 limb and augmented leads also allows for accurate measurement of the standard ECG interval duration measurements in most cases, which is extremely valuable during clinical trials, where detection of changes in QTc (as well as other measurements) is critical to maintaining patient safety as well as for program-wide assessments of drug-related effects. There are cases where measurements cannot be performed in the limb leads due to artifact or abnormal T wave morphology, and where a full 12-lead ECG is necessary, but in most cases, high quality interval measurements are feasible. Most important, a 6-lead ECG can simply be collected by a patient at home, without need for medical supervision or special training – enabling collection of ECG data and measurements in a truly remote setting.

In contrast, even 6-lead recordings of the limb leads are often not adequate for a full assessment of the cardiac safety of a new compound. Anterior wall ischemia or infarction, ventricular hypertrophy, Brugada Syndrome, and many other cardiac abnormalities require evaluation of the precordial leads for diagnosis.

12-lead ECG recordings (standard 10 second recordings)

The standard 12-lead ECG machine records 10 seconds of each lead at very high resolution (500-2000 samples per second), and these recordings are the gold standard for cardiologic evaluation. 12-lead recordings allow measurement of ECG intervals even when the limb leads are suboptimal, and allow detection of many cardiac abnormalities that are invisible to the limb leads. 12-lead ECGs are the mainstay of clinical practice as well as of clinical trials. Newer technologies that make collection of 12-lead ECGs in the clinic setting simpler, or even at home by the patient, are certainly welcome. The ability for a patient to record a full 12-lead ECG at home, without medical supervision, would have many potential uses during clinical trials.

12-lead continuous ECG recordings (12 lead holter)

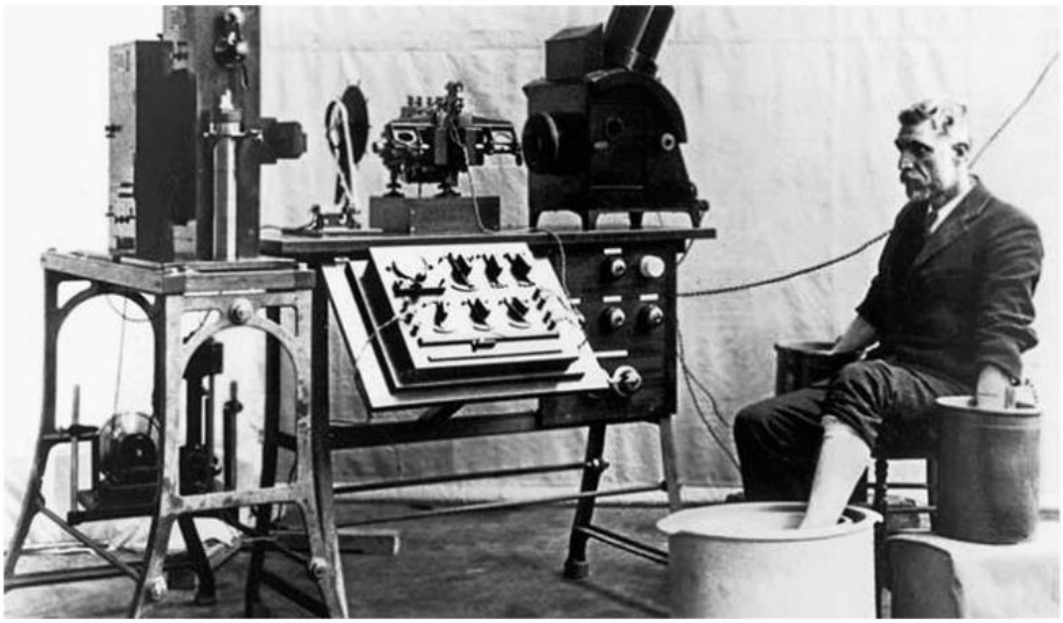
Continuous 12-lead holter recordings are typically worn for 24-48 hours, and enable collection of continuous full 12-lead ECGs over a course of days. One can use these for arrhythmia monitoring, as with a single lead continuous recorder, but one may also extract 10 second 12-

lead ECGs at any point during the recording period. These are equivalent to standard 12-lead ECGs collected with a standard 12-lead ECG device, and are particularly useful when multiple ECGs are collected over a short period of a few hours to a full day. In many clinical trials, 3-10 ECGs may be required at each timepoint, with up to 15 ECG timepoints over a single day. This is quite common in dedicated QT trials, as well as in many SAD/MAD studies conducted during the early phase of a drug development program. Besides collecting data for the entire 24-48 hours, the devices simplify ECG collection for the sites. Instead of having to record 3-10 ECGs many times during a day, the site simply needs to hook up the device at the beginning of the recording period, and then take it off at the very end (plus making sure that the leads remain connected properly). Full 12-lead ECGs can then subsequently be retrospectively extracted at any timepoint from this continuous recording, wherever required. The 12-lead continuous recorders have become the standard of practice in drug trials that require many ECG collections during a short period of time, such as Thorough QT/QTc trials (TQTs), and in early phase QT assessment strategies.

12-lead ECGs: Still the Gold Standard

Despite the proliferation of new ECG technologies, the 10 second 12-lead ECG remains the standard tool for use in clinical medicine as well as in clinical trials. The newer technologies have expanded our ability to record for longer periods of time (helpful for capturing infrequent events) or have enabled collection of limited lead ECGs outside of the medical setting (enabling patients to record limited ECG recordings at home or even when in public). However, it's critical to recognize the limitations of limited lead devices. If you go to the emergency room because you have chest tightness, will the ER perform a single lead or 6-lead ECG? Of course not. If you see a cardiologist because you've developed shortness of breath with mild exercise, would the cardiologist order a 14 day patch recording? Of course not. The 12-lead ECG includes the precordial leads, which are essential for detection of so many cardiac issues both in clinical practice as well as in clinical trials. In the clinical trial space, we have become hyperfocused on collecting cardiac interval duration measurements, and expressly on monitoring the QT interval. Yet drug induced QT prolongation represents only a tiny fraction of potential drug induced cardiac adverse events. ECG measurements are necessary – but will not help detect drug induced cardiac toxicities such as ischemia, myocardial infarction, pericarditis, direct cardiotoxicity that can produce heart failure, Brugada Syndrome, or valvular dysfunction. ECG interval duration measurements alone will not help detect progression of a patient's underlying cardiac disease (unrelated to medications), though preexistent cardiac disease is common in older patients.

It's important to recall that no new drug approved since 2005 (the year that the ICH E14 Guidance was ratified and went into effect in the US, EU, and Canada) has been recalled due to QT prolongation or concerns about drug induced sudden cardiac death. However, numerous new drugs have been abandoned during development or have been recalled after approval due to non-QT related cardiac toxicity. Full 12-lead ECGs are essential for detecting these cardiac toxicities early in drug development, not late in Phase 3 or after drug approval. Just as in carpentry, it's important to use the right tool for the right job. The more tools in your toolkit, the more options available – but trying to use a screwdriver to drive in a nail doesn't work very well. With the proliferation of ECG technologies, it's critical to match the need with the correct ECG collection method.



Dr Einthoven's ECG recorder *(no longer available from ERT)*

WHEN ARE 6-LEAD VS. 12-LEAD ECGS APPROPRIATE?

Use Case for 6-Lead ECGs

6-lead ECGs are, by definition, incomplete when compared to complete 12-lead ECGs. However, since the KardiaMobile 6-lead ECG device is very easy to use for most people without medical backgrounds, and requires minimal training, there are situations in which it may

be very useful. The 6L device is currently approved for detecting the presence of normal sinus rhythm, atrial fibrillation, bradycardia, tachycardia, and other rhythm disturbances. However, since it is recording a standard set of ECG limb leads (leads I, II, III, aVR, aVL, and aVF), a physician may be able to detect additional rhythm or conduction disturbances. Since the device records standard limb leads, a physician may also use these recordings to measure standard cardiac intervals (heart rate, PR interval, QRS duration, and QT interval), and thus permits calculation of QTc (QT interval corrected for heart rate).

When might this be useful?

In clinical trials, a 6-lead recording is often sufficient for assessing the cardiac rhythm and for measuring the standard interval duration measurements, which are usually measured on lead II. During a clinical trial, a patient who is remote from the investigational site can use the 6-lead device to record a 6-lead ECG at any time, either for a regularly scheduled assessment or as an unscheduled ECG during symptoms, and can then send the ECG to the site for evaluation. This is not as good as having a full 12-lead ECG, but it is far better than having no data at all. During clinical trials, this approach can be used when patients are unable to travel to the investigational site and are unable to obtain a full 12-lead ECG locally. These 6-lead ECGs may allow detection of many cardiac arrhythmias, and can often be used for detection of drug related QTc prolongation. While the measurements may not have the precision that we typically use for dedicated QTc studies (such as the Thorough QT/QTc trial, or TQT), the 6-lead recording measurements can often be used to detect large, potentially dangerous increases in QTc (or other measurements), even if not as precise as high precision QT assessments. 6-lead ECGs collected when a patient is symptomatic while at home may also allow diagnosis of new onset atrial fibrillation or supraventricular tachycardia, and may even be adequate to discriminate between ventricular tachyarrhythmias and supraventricular rhythms with aberrancy.

A simple observation: 6 leads are better than 1 lead, and are far superior to no ECG data at all.

Use Case of 12-lead ECGs: Why 6-lead ECGs Cannot Replace the 12-lead ECG

While the 6-lead ECG device offers new opportunities to collect valuable ECG data from patients at home that would otherwise be unavailable, they have their limitations. As an analogy, if you went to a dermatologist because of a family history of skin cancer, would you want the dermatologist to only examine your back, and not your entire body? While many of us are somewhat squeamish about having a stranger examine our entire body with a magnifying glass, we understand that the dermatologist needs to be able to check our entire body, since skin cancer can occur anywhere. Similarly, the 6-lead ECG

only allows the physician reader to view data from a limited region of the heart – but may allow almost no view of data from other regions. Therefore, 6-lead ECGs may allow detection of only a fraction of cases of some cardiac problems, but may have no value whatsoever for detecting certain other cardiac issues.

6-lead ECGs may have limited usefulness for detecting the following conditions:

- Myocardial ischemia (primarily inferior wall)
- Myocardial infarction (primarily inferior wall)
- Electrolyte abnormalities
- Pericarditis
- Cardiomyopathic processes
- Wolff-Parkinson-White Syndrome
- Early Repolarization Syndrome

6-lead ECGs have almost no ability to detect some other serious cardiac conditions:

- Hypertrophic Cardiomyopathy
- Left ventricular hypertrophy
- Right ventricular hypertrophy
- Anterior wall ischemia
- Anterior wall myocardial infarction
- Right ventricular myocardial infarction

Brugada Syndrome

Arrhythmogenic RV Dysplasia

Atrial enlargement

SUMMARY

There are currently many different ECG solutions that are available for use in clinical trial – leading to confusion about which modalities are appropriate for which uses. These range from single lead devices that record for brief intervals to 12 lead devices that can record for 24 hours or longer. Each of these modalities has its own place within clinical trials. The standard 12-lead ECG remains the most appropriate ECG modality for most routine uses, while continuous recordings (patch or holter) and limited lead devices (single through 6-lead) have their own specific niches.

BIOS

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Dr. Robert Kleiman is a cardiac electrophysiologist who has performed research in both basic cellular electrophysiology as well as clinical electrophysiology. Dr. Kleiman trained at the University of Pennsylvania and practiced clinical cardiology for 12 years before joining ERT in 2003. Dr. Kleiman currently oversees all of ERT's cardiology services, consulting with external clients and providing cardiac safety regulatory advice.

Todd Rudo, MD
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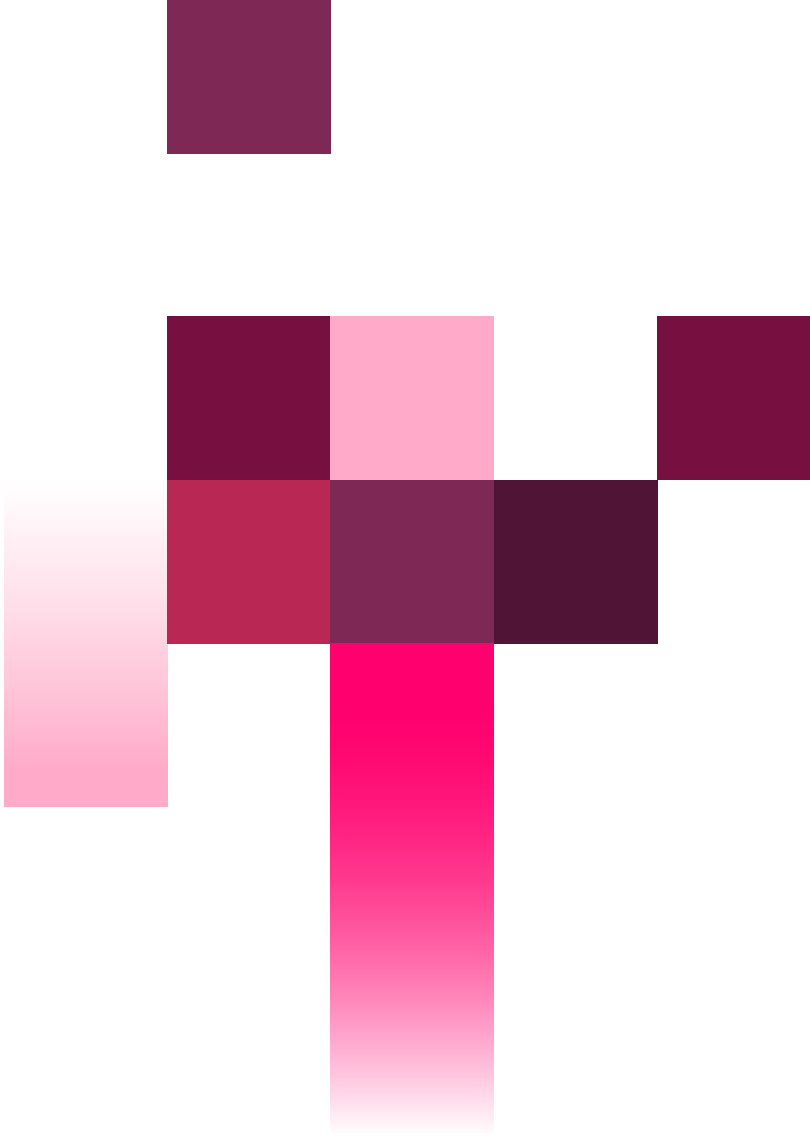
Dr. Todd Rudo is the Deputy Chief Medical Officer at ERT, with board certifications in cardiology, cardiac electrophysiology, nuclear cardiology, and adult echocardiography. He completed his general medical training at Jefferson Medical College in Philadelphia, PA, and specialty training at Lankenau Medical Center in Wynnewood, PA. After transitioning from private practice, Dr. Rudo has focused his career on drug safety / pharmacovigilance with responsibilities across multiple therapeutic areas within large and medium-size pharmaceutical companies. In his current role, he primarily supports cardiac safety consultative services, in addition to oversight of ECG core lab activities.



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