# Nuclear Imaging: Physician Confusion Over True Quantification and Isotope Redistribution

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**Abstract**

**Clinicians are beginning to understand the importance of quantification for use in medicine, particularly nuclear medicine. With the recent introduction of mandates by CMS, ASNC, and the SNMMI for quantification, it is not surprising that professional papers are beginning to be published on the topic. One recent publication paper by Zhao et al. demonstrates the misunderstanding that is plaguing the field of modern nuclear medicine. The second publication by Dorbala et al. discusses a major flaw in the current understanding of redistribution measurements of isotopes such as Sestamibi and Tetrofsomin.**

**Keywords:** *FMTVDM; True nuclear quantification; Isotope redistribution; Health-spectrum*

## The Current Misunderstanding of Quantification

Quantification is not asking whether a tool can count or provide "a number or ratio" to what is being seen on an image, but rather whether the tool being used can count "accurately". In the Zhao paper, the authors present several methods using phantoms and display "counts" of isotope scintillation activity and reported on the ability of the cameras being used to count. They concluded that there is a camera calibration factor which must be applied - with one such example in the paper being the counts obtained using a point source with a single photon emission computed tomography (SPECT) camera using a 128 × 128 matrix. The remainder of this paper is applicable to all of the discussion in these papers [1,2].

Herein lies a fundamental problem with both physician communication and definitions erroneously being used today - terminology which needs to be corrected before we can fully understand what nuclear imaging quantification truly is.

Quantification determination of a nuclear image is not merely a matter of asking whether the camera (our scintillation measuring tool) can count. This is like asking a child to count and the child nods and then says 1,2,3,6,9,5,14, etc. Yes, the child can count - just not correctly or accurately.

Qualitative imaging produces a yes/no phenomena by the person interpreting the test result. Yes - the interpretation reports disease is present; or no - the interpreter doesn't believe disease is present. The consequence of this approach results in sensitivity and specificity problems.

Calibration/standardization of nuclear cameras (tools which measure scintillation), enhancement of tissue differences, and quantitative measurement of those differences for diagnostic-and-treatment monitoring purposes, are possible using The Fleming Method (TFM$^{©®}$). TFM is the first component of the Utility Patent [3,4] "The Fleming Method for Tissue and Vascular Differentiation and Metabolism" (FMTVDM, patent #9566037), which makes it possible to measure - accurately, consistently, and reproducibly - these differences without manipulating the data with mathematical models that artificially massage (rather than measure) the data.

As recently presented [5] and as published [6-10], for our scintillation tools to be accurate, consistent, and reproducible around the world, we must be able to calibrate these tools (nuclear cameras) to a known standard. Standards are constant and unchanging. It doesn't matter whether we are talking about a length, weight, unit of time, or scintillation; a standard for a measuring tool must be absolutely unchanging and established for the resulting quantification measurement to be considered accurate, consistent, and reproducible - thereby allowing use of the calibrated measuring tool anywhere in the world at any time yielding the exact same measurement without variance. The standardization (TFM) is dependent upon the tool and the known standard as defined by the FMTVDM. Anything less is simply the child inaccurately and unreliably counting.



**Figure 1:** Standardization (calibration) is contingent upon understanding the type of nuclear camera being used, which in turn is dependent upon the isotope being used, which in turn is dependent upon what is being studied.

FMTVDM provides the first-and-only method detailing how this standardization/calibration process must be carried out. TFM nuclear cameras are quantitatively calibrated using the applicable isotope based upon what is being imaged (e.g. heart, breast, etc.) and the type of nuclear camera being used (Figure 1-Figure 4).
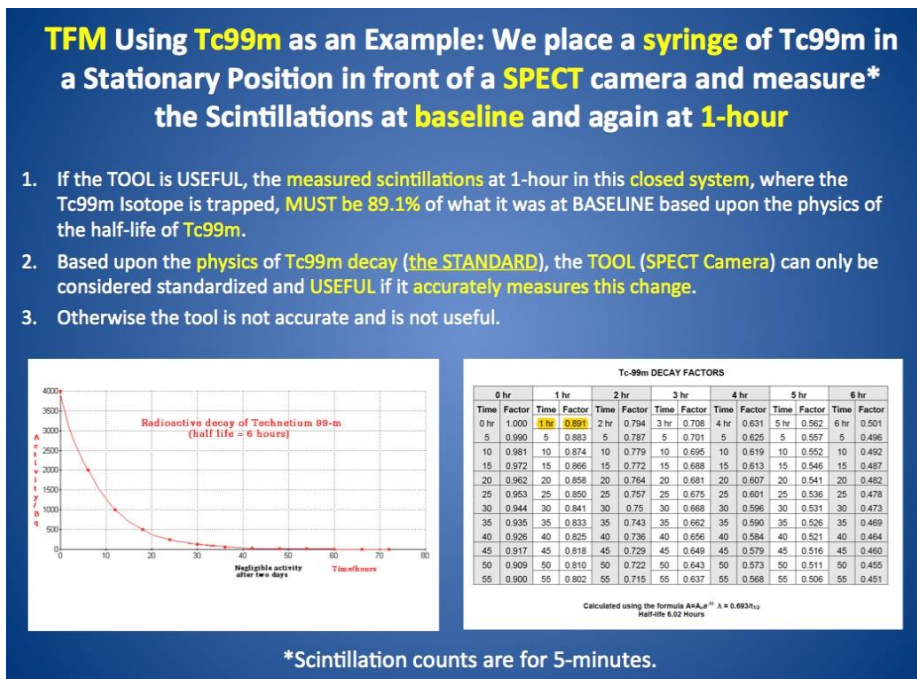
**TFM Using Tc99m as an Example: We place a syringe of Tc99m in a Stationary Position in front of a SPECT camera and measure* the Scintillations at baseline and again at 1-hour**

1. If the TOOL is USEFUL, the measured scintillations at 1-hour in this closed system, where the Tc99m Isotope is trapped, MUST be 89.1% of what it was at BASELINE based upon the physics of the half-life of Tc99m.
2. Based upon the physics of Tc99m decay (the STANDARD), the TOOL (SPECT Camera) can only be considered standardized and USEFUL if it accurately measures this change.
3. Otherwise the tool is not accurate and is not useful.

Radioactive decay of Technetium 99-m (half life = 6 hours)

Negligible activity after two days

Time/hours

Tc-99m DECAY FACTORS

| 0 hr Time | 0 hr Factor | 1 hr Time | 1 hr Factor | 2 hr Time | 2 hr Factor | 3 hr Time | 3 hr Factor | 4 hr Time | 4 hr Factor | 5 hr Time | 5 hr Factor | 6 hr Time | 6 hr Factor |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 hr | 1.000 | 1 hr | 0.891 | 2 hr | 0.794 | 3 hr | 0.708 | 4 hr | 0.631 | 5 hr | 0.562 | 6 hr | 0.501 |
| 5 | 0.990 | 5 | 0.883 | 5 | 0.787 | 5 | 0.701 | 5 | 0.625 | 5 | 0.557 | 5 | 0.496 |
| 10 | 0.981 | 10 | 0.874 | 10 | 0.779 | 10 | 0.695 | 10 | 0.619 | 10 | 0.552 | 10 | 0.492 |
| 15 | 0.972 | 15 | 0.866 | 15 | 0.772 | 15 | 0.688 | 15 | 0.613 | 15 | 0.546 | 15 | 0.487 |
| 20 | 0.962 | 20 | 0.858 | 20 | 0.764 | 20 | 0.681 | 20 | 0.607 | 20 | 0.541 | 20 | 0.482 |
| 25 | 0.953 | 25 | 0.850 | 25 | 0.757 | 25 | 0.675 | 25 | 0.601 | 25 | 0.536 | 25 | 0.478 |
| 30 | 0.944 | 30 | 0.841 | 30 | 0.75 | 30 | 0.668 | 30 | 0.596 | 30 | 0.531 | 30 | 0.473 |
| 35 | 0.935 | 35 | 0.833 | 35 | 0.743 | 35 | 0.662 | 35 | 0.590 | 35 | 0.526 | 35 | 0.469 |
| 40 | 0.926 | 40 | 0.825 | 40 | 0.736 | 40 | 0.656 | 40 | 0.584 | 40 | 0.521 | 40 | 0.464 |
| 45 | 0.917 | 45 | 0.818 | 45 | 0.729 | 45 | 0.649 | 45 | 0.579 | 45 | 0.516 | 45 | 0.460 |
| 50 | 0.909 | 50 | 0.810 | 50 | 0.722 | 50 | 0.643 | 50 | 0.573 | 50 | 0.511 | 50 | 0.455 |
| 55 | 0.900 | 55 | 0.802 | 55 | 0.715 | 55 | 0.637 | 55 | 0.568 | 55 | 0.506 | 55 | 0.451 |

Calculated using the formula A=A₀e⁻ᵏᵗ λ = 0.693/t₁/₂
Half-life 6.02 Hours

*Scintillation counts are for 5-minutes.

**Figure 2:** Isotope decay is the physical constant against which nuclear cameras can be calibrated to guarantee that the nuclear camera can accurately, consistently and reproducibly measure changes in isotope emission; thus, providing a tool which will quantitatively measure the same outcome independent upon time or place.
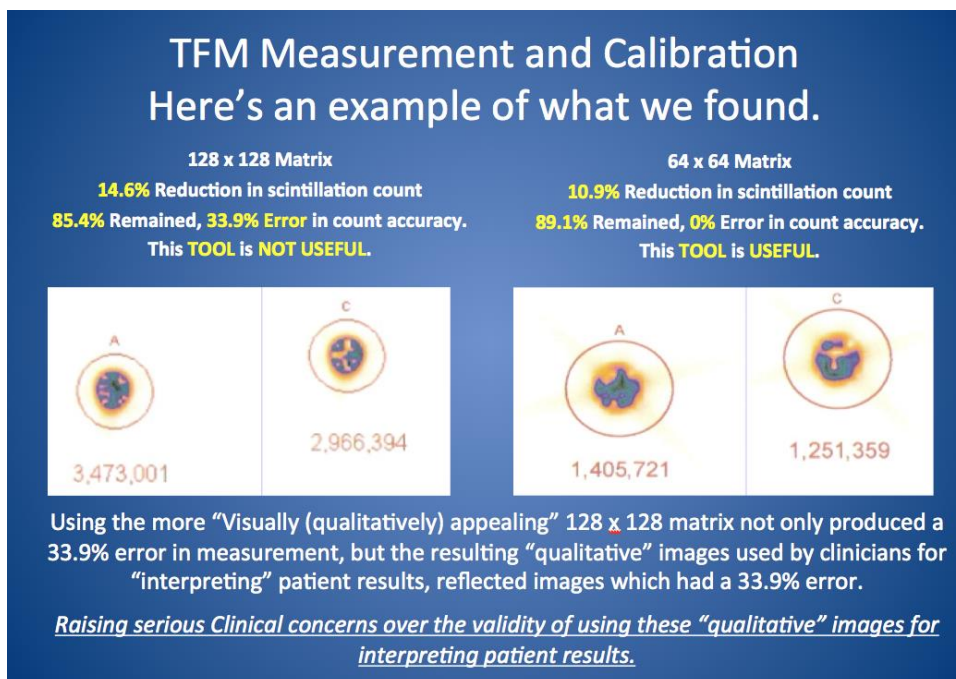
**TFM Measurement and Calibration Here's an example of what we found.**

**128 x 128 Matrix**
14.6% Reduction in scintillation count
85.4% Remained, 33.9% Error in count accuracy.
This TOOL is NOT USEFUL.

**64 x 64 Matrix**
10.9% Reduction in scintillation count
89.1% Remained, 0% Error in count accuracy.
This TOOL is USEFUL.

3,473,001    2,966,394

1,405,721    1,251,359

Using the more "Visually (qualitatively) appealing" 128 x 128 matrix not only produced a 33.9% error in measurement, but the resulting "qualitative" images used by clinicians for "interpreting" patient results, reflected images which had a 33.9% error.

*Raising serious Clinical concerns over the validity of using these "qualitative" images for interpreting patient results.*

**Figure 3:** Demonstration of how nuclear cameras may be presumed to be accurate, yet are not actually correctly measuring isotope emissions, making the results unreliable.
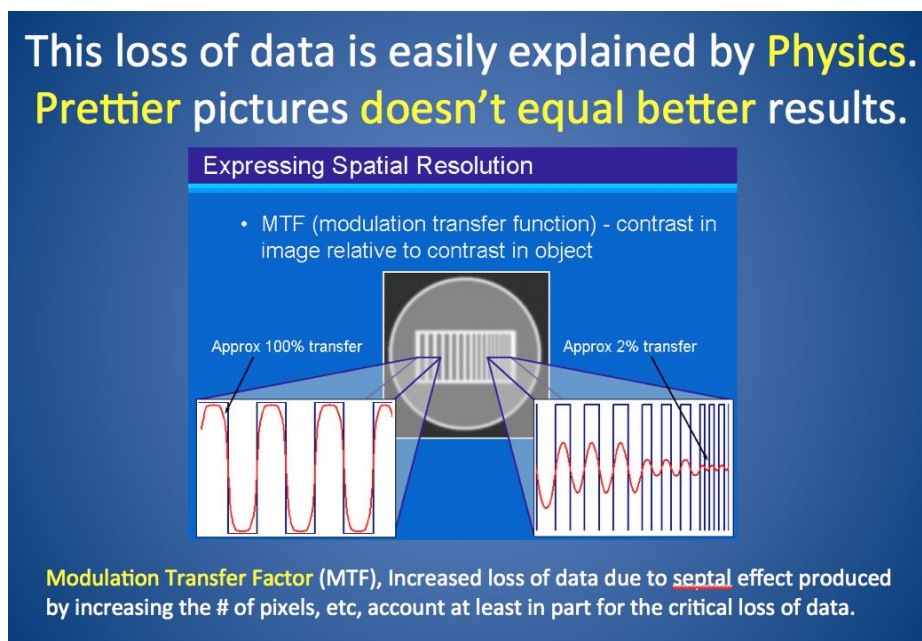
**Figure 4:** Multiple factors account for errors in nuclear cameras, making the cameras unreliable without calibration (TFM). By conducting TFM, there errors can be eliminated, making it possible to use nuclear cameras to quantitatively measure isotope emissions (scintillations) and more importantly, changes in isotope emissions (redistribution) over time.

An example of such measurement errors absent calibration using TFM in nuclear cameras is particularly germane given the Zhao [1] paper. Zhao reported on a point source for a SPECT camera using a $128 \times 128$ matrix. Figure 1- Figure 4 were presented at the 2018 Florida Society of Nuclear Medicine Technology (FNMT) meeting [4]. Figure 3 shows the errors associated with simply pointing a SPECT (or PET) camera at an object and asking the camera to count/measure scintillations without "quantitatively" standardizing the camera first (TFM). The $128 \times 128$ matrix, which had passed "qualitative" control (QC), revealed an error of 33.9%. The flawed scintillation count not only cannot provide true quantitative results (including measuring actual isotope redistribution), but its subsequent value for qualitative imaging presents further diagnostic concerns given the lost information unavailable for the clinician to use in the interpretation of the results.

As shown in Figure 3, when the SPECT camera was asked to count the emissions (scintillations) from technetium – 99 m sample using the $128 \times 128$ matrix setting for this particular camera, there was a 14.6% reduction in scintillation quantification over a 55-minute period of time. Given the actual physical decay of isotope, this represents an error of 33.9%. Had the camera been correctly calibrated (TFM) - as it was in the right half of Figure 3 - there would have been a 10.9% reduction in scintillation measurement. The physics of isotope decay do not change and are therefore the standard against which TFM calibrates. As a result, while the $128 \times 128$ matrix setting may have appeared more visually appealing, it did so at the loss of almost 34% of the data, making it diagnostically inadequate.

True quantification cannot be presumed merely because we place a radioactive isotope in front of the field of view of our nuclear cameras. The fact that we are able to see scintillation counts does not mean those counts are accurate. Detection is not measurement. Our nuclear cameras, like any other tool, must be calibrated against a known standard for them to be accurate, consistent, and reproducible. Anything less produces a result which is unreliable. FMTVDM©℗ provides TFM©℗ for

scintillation device (planar, SPECT, PET, handheld probes, etc.) standardization, necessary to assure true quantification of the acquired results.

It is important that our quantification of isotope scintillation be more than simply a question of "can our cameras count scintillations". It must be a matter of whether our nuclear cameras can accurately, consistently, and reproducibly count the actual numbers of scintillations occurring - something which can only be done using a calibrated nuclear camera which has been standardized against the known standard of isotope decay. This allows us to calibrate the camera to match reality.

FMTVDM is the only method which accurately standardizes our nuclear cameras (TFM) utilized in nuclear medicine and physics. TFM$^{©®}$, is applicable to any device measuring scintillations, independent of isotope, including inter alia PET, SPECT, handheld probes. It is not limited to SPECT cameras or Tc99m isotopes.

**The Misunderstanding of Sestamibi and Tetrofosmin Redistribution**

As with the paper by Zhao [1] there is unfortunately nothing within the currently submitted guidelines [2] which addresses the lack of true quantification and the detailed discussion of qualitative control which, while important, does not compensate for failure to quantitatively standardize [3-10] myocardial perfusion or any other nuclear scintigraphy imaging (including, but not limited to, handheld probes, planar, SPECT or PET imaging). In fact, as shown in Figure 1- Figure 4, failure to have the necessary quantitative standardization ultimately leads to a failure in qualitative imaging, no matter how much attention is placed on "qualitative control" (QC).

Since most of this has been discussed supra, we will turn our attention to the statement made under the "Delay Time for Imaging" statement on page 19 of Dorbala [2].

> "In contrast, the properties of 99mTc Sestamibi and 99mTc Tetrofosmin, particularly the lack of clinically significant redistribution or washout, allow delayed imaging and, therefore, permit stress testing and tracer injection to take place at a location remote from the imaging laboratory. Image acquisition can simply be repeated when patient motion or extracardiac tracer uptake is considered responsible for the production of a perfusion defect. The standard delay between injection of 99mTc Sestamibi or 99mTc Tetrofosmin and scan is 30 to 60 minutes for rest and 15 to 60 minutes for stress (the former for exercise stress)."

It is somewhat reassuring that the authors are no longer saying Sestamibi and Tetrofosmin do not redistribute. The language in the package inserts has softened over the last decade from there is "no redistribution" in people to "definitive human studies to demonstrate possible redistribution have not been reported". It is clear that neither the companies who make and sell these drugs, nor the authors, have read the studies published showing the "definitive human studies" on the clinical importance of Sestamibi and Tetrofosmin [3-19] redistribution.

One of the very fundamental problems here is that the use of two injected doses of either Sestamibi or Tetrofosmin done at "rest" and "stress" cannot possibly look for redistribution of either one of these injected doses of isotope, as there is no way to differentiate the effect of one injected dose from the other. Redistribution is, by its very definition, the movement of a single injected dose of isotope over a period of time reflecting differences in uptake, retention, and release of the isotope from the

tissue being studied - which, in myocardial perfusion imaging (MPI), is cardiac tissue. Such redistribution reflects changes from "normal" tissue vascularity and viability to abnormal diseased tissue (which, after all, is why the studies are being done).
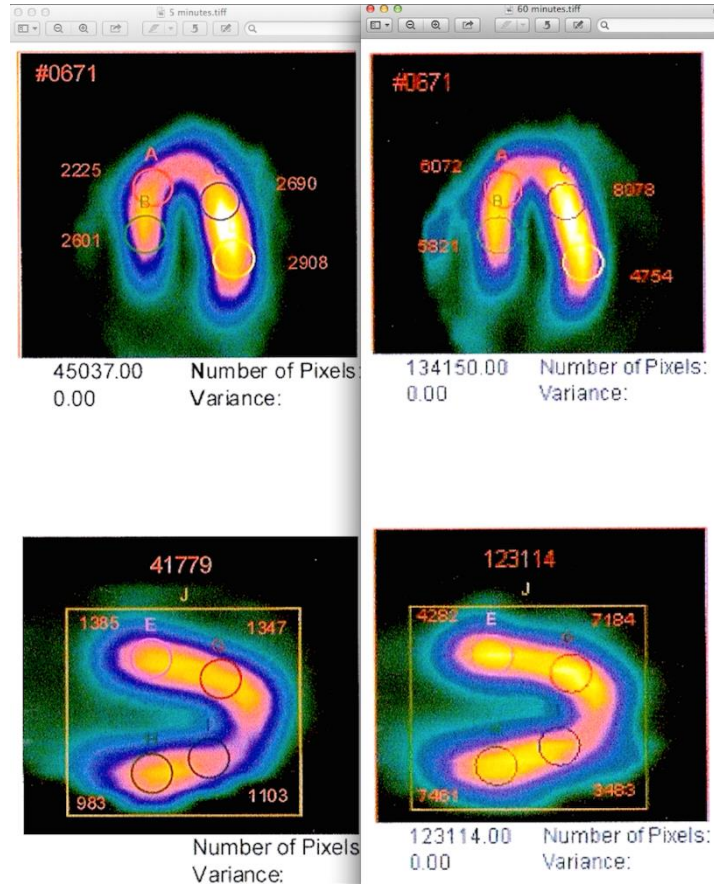


**Figure 5:** FMTVDM True Quantification of serial measurements of isotope redistribution.

**Note:** Image displays in horizontal (top) and vertical (bottom) long axis views show True Quantification measurements of sestamibi redistribution using FMTVDM©®. While each reconstructed image revealed "qualitatively" normal appearing MPI, the True Quantification measurements showed lower sestamibi counts in each myocardial region at 5-minutes post stress (left panels) isotope injection compared with the 60-minute post-stress image acquisitions following a single injected dose of sestamibi with "stress". The results measured "wash-in" seen with vulnerable inflammatory plaques and critically narrowed arteries. This True (not virtual) Quantification demonstrated triple vessel coronary artery disease in this individual requiring intervention.

An example of the flaws permitted using a purely visual qualitative interpretation of sequential images is shown in Figure 5. Here Sestamibi redistribution is quantitatively obvious from the measurements obtained following nuclear camera calibration (TFM) - a necessary component to obtain true quantification of isotope redistribution that is missing from both the Zhao [1] and Dorbala [2] papers. The visual images themselves in Figure 5 would suggest there was no redistribution; however, as shown from the actual measurements, such a failure to recognize the redistribution could have cost the patient his life.

To further understand what has happened in the history of nuclear cardiology and where the argument came from that Sestamibi and eventually Tetrofosmin do not redistribute, one needs to be aware of what has actually transpired and the battle for "market share" and "money" [17,18].

In an effort to improve the qualitative imaging seen with Tl-201 imaging, a new generation of isotopes utilizing Tc-99m (metastable) were developed. Initially, this resulted in the introduction of two competing isotopes: one named 99mTc-6-methoxylisobutylisonitrile, originally known as RP-30A and subsequently known as Cardiolite and later Sestamibi or just plain MIBI. The other imaging agent, a boronic acid adduct of technetium oxime (BATO), which the lead author of this paper wrote the first SPECT [20] paper on, was initially called SQ30217 (Squibb Diagnostics). SQ30217 later became known as Cardiotec (*vs.* Cardiolite) and later Teboroxime or just plain TEBO (*vs.* MIBI).

All of these name changes were made to help market the isotopes and find a way to make each isotope more competitive with the other. The advantage and disadvantage of TEBO was that it appeared to be more rapidly extracted from the blood and taken up by cardiac tissue. This made it necessary to image patients within the first two minutes following stress injection of the isotope - a property which was initially thought to be its great advantage proved to be its Achilles' heel. The other pharmaceutical company (DuPont) learned early on that this placed a great stress on nuclear imaging departments which in those days had fewer cameras and were still trying to use the cameras for multiple nuclear studies - not just cardiac.

The companies making and selling Sestamibi (sequentially DuPont, BMS, then Lantheus) have taken advantage of this and told physicians and hospitals that using Sestamibi would be logistically easier to use - that the nuclear departments would not need to worry about imaging timing issues. The sales pitch was Sestamibi would give the same result at one-hour or four-hour post-stress injection and you did not need to image right away as TEBO required. Nuclear departments could schedule patients at will and know that Sestamibi did not have the time constraints Teboroxime did, simplifying the lives of those working in the nuclear departments.

In the end this worked - it worked so well, in fact, that TEBO is no longer used in the USA. But MIBI is, and by telling physicians and hospitals that they could do the MIBI study anywhere between one hour and four hours, the greatest problem became one of how to get a "rest" and "stress" study done in the same day. The fallacy of "rest-stress" imaging has already been discussed supra and in the references [3-10]. The makers of MIBI were now free to sell two doses of Sestamibi instead of just one. This means when you do the math (since the "rest" dose is typically $1/3^{rd}$ of the "stress" dose), the company is able to make three-to-four times the profit by selling three resting doses equaling the same price as a single "stress" dose (8-10 *vs.* 24-30 mCi).

Even the primary author initially bought into the concept of "rest-stress" imaging and admittedly has written medical textbook chapters [22,23] on how "stress-rest" imaging should be done. Subsequent publications (such as this one) have corrected that mistake. Fortunately, the lead writer remembered what his medical school dean told his entering class during their first day of orientation at the University of Iowa: "90% of what we will teach you is wrong - we simply do not know what that 90% is". Our dean encouraged those of us interested in doing the necessary research to find the answers, which would make medicine better.

The primary author has spent decades attempting to do just that, questioning and investigating that which he was taught about stress-rest imaging, about isotope redistribution, about quantification (including both coronary arteriography, and myocardial perfusion imaging), about the causes of coronary artery disease and angina, and about cancer, diets, and inflammation.

With the Sestamibi companies having successfully taken their stance and without quantification to find the redistribution characteristics of Sestamibi, these corporations have profited from this for almost three decades. When Tetrofosmin came onto the market, it simply repeated the same marketing approach.

Efforts to correct this by others and the primary author have been largely - although not completely - ignored [17-19]. It is true that the Sestamibi package insert no longer claims Sestamibi does not redistribute; however, the company fails to acknowledge the clinical importance of redistribution in people or that the initial redistribution occurs within minutes and not hours. The tradition of how Sestamibi and Tetrofosmin are used (waiting one hour after stress and resting doses to image the patient) was so ingrained in the medical practice of myocardial perfusion imaging (MPI) following the original publication by Wackers et al [24] that few [1,2] have ever questioned it; still, others have [3-21].

The companies which make and sell Sestamibi and Tetrofosmin have continued to follow the primary author's presentations including SNMMI conferences [24-37], where physicians and scientists have not only received CME credits for attending these presentations but have also subsequently returned to present their own replication studies showing redistribution of these isotopes [36]. For these companies to continue to hold the position that there is insufficient information to demonstrate the clinical importance of isotope redistribution is disingenuous - particularly given the company's correspondence [17], which no longer denies the redistribution of these isotopes.

## Conclusion

The old era of qualitative Nuclear Cardiology and Nuclear Medicine has been limited by the use of qualitative interpretation of image results, following efforts at qualitative control and the inability to produce either quantitative standardization or quantitative results.

Failure to follow quantitative standardization/calibration (TFM) and quantitative measurement of redistribution of isotopes may have been profitable for the pharmaceutical and camera equipment companies up to this point, but that era has ended. The world has changed and the demand for something superior has been met with FMTVDM$^{©®}$. FMTVDM$^{©®}$ answered at least one of the errors we were taught in medical school and with it begins the dawn of the 21$^{st}$ century of Nuclear Cardiology & Nuclear Medicine.

As demonstrated in Figure 1 - Figure 5, FMTVDM$^{©®}$ is not fooled by erroneous visual interpretation of images. Real disease and redistribution can be measured without doubt or error. The introduction of FMTVDM$^{©®}$ provides the first and only quantitative Nuclear Cardiology & Nuclear Medicine imaging method, which along with proprietary equations provides differentiation of tissue based upon metabolic and regional blood flow differences which can be enhanced and measured finding transitional changes in disease [37]. The era of patient-oriented and patient-focused treatment based upon quantitative outcomes' data is here. The era of confusion to understand the redistribution properties of all isotopes and the confusion as to how to measure them has finally ended.

## Conflict of Interest

FMTVDM was issued to the primary author. All figures reproduced with his expressed consent.

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