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Mapping the Predicate Chain of 510(k) Devices

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Suppose you have the perfect cup of coffee. Taste it. Now add just a granule of sugar. Can you taste the difference? Probably not. Repeating this exercise is unlikely to cause a perceivable difference in how the coffee tastes. Applying the *transitive law*[1] in mathematics tells us that if each tasting is effectively the same as the last, then the first cup of coffee must also be effectively the same as one that follows thousands of additional granules of sugar. Common sense, however, tells us that this is not true. At some point there will be a noticeable difference between tastings. While the transitive law is appropriate for numbers because they are constant, it is not necessarily appropriate in non-numerical settings. This analogy parallels an often-stated concern with the medical device approval pathway in the U.S., known as Premarket Notification 510(k), that has permitted hundreds of thousands of medical devices to reach the U.S. marketplace for several decades.

Devices cleared under Premarket Notification 510(k), often referred to as PMN or 510(k),[2] must "demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent,[3] to a legally marketed device (section 513(i)(1)(A) FD&C Act)."[4] A legally marketed device on which equivalence is drawn is referred to as a predicate device and defined by the U.S. Food and Drug Administration (FDA) as a device that:[5]

- was legally marketed prior to May 28, 1976 (referred to as a "preamendments device");[6]
- has been reclassified from Class III to Class II or I;
- has been found substantially equivalent through the 510(k) pathway; or
- was granted marketing authorization via the De Novo classification process under section 513(f)(2) of the FD&C Act. The De Novo classification process provides a pathway for which

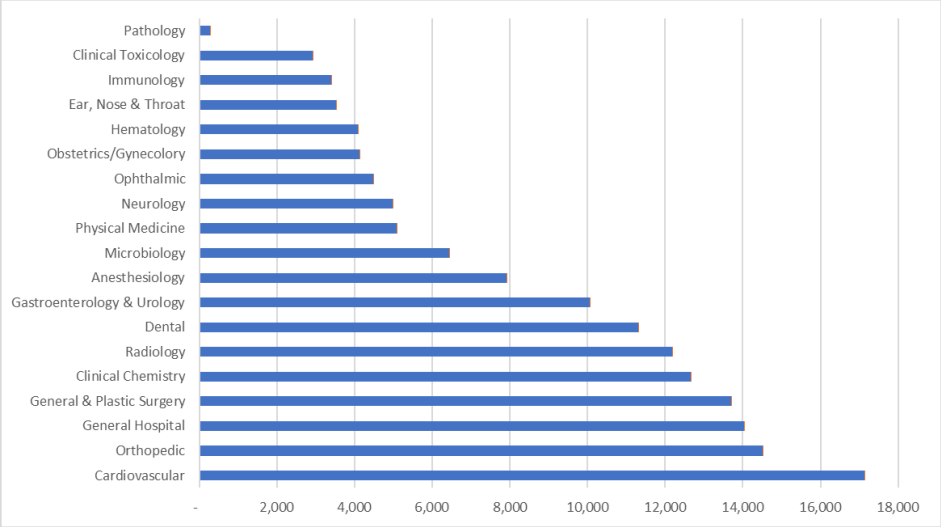
> general controls or general and special controls provide a reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device.[7]

A common criticism of the 510(k) pathway is that it can create so-called approval chains of devices that reach the marketplace without recent clinical testing. For example, critics in the Netflix Original documentary, "The Bleeding Edge," contended that current medical devices have become much more complex but testing requirements have not evolved along with them. Dr. David Kessler, current Chief Science Officer of Covid-19 Response Team and former FDA commissioner,[8] states in the documentary that "[the 510(k)] provision, which was meant as an exception, in essence [is] a loophole" for most devices.[9]

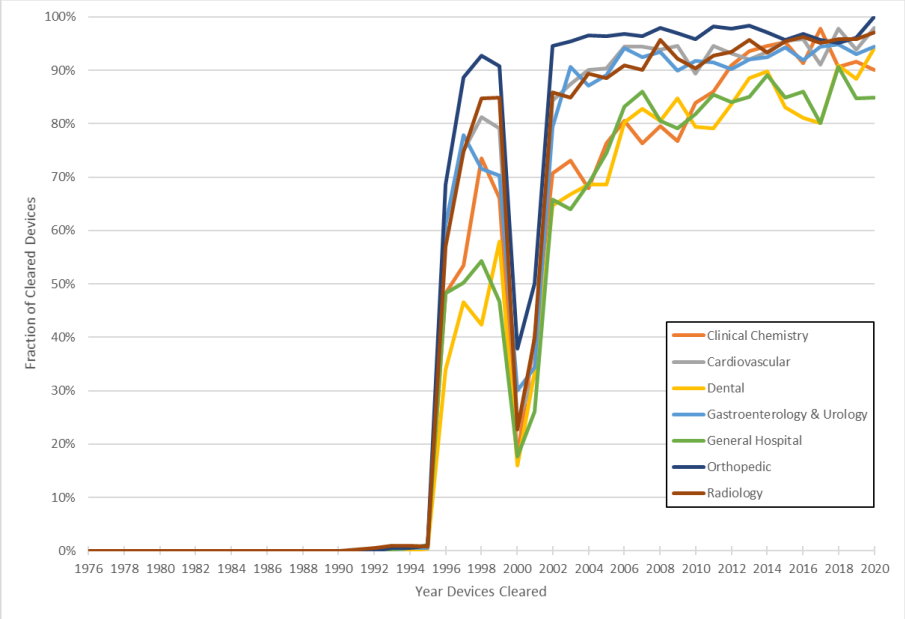
This article sheds some light on this topic by analyzing a uniquely assembled dataset that combines publicly available datasets of devices cleared under the 510(k) pathway from 1976 to 2020[10] and an additional dataset that identifies the predicate devices for cleared devices when available. The latter dataset was constructed by Emerging Health LLC using tens of thousands of documents from a searchable FDA database of devices cleared under the 510(k) pathway and scouring the documents for identifying predicate information using a computer algorithm.[11]

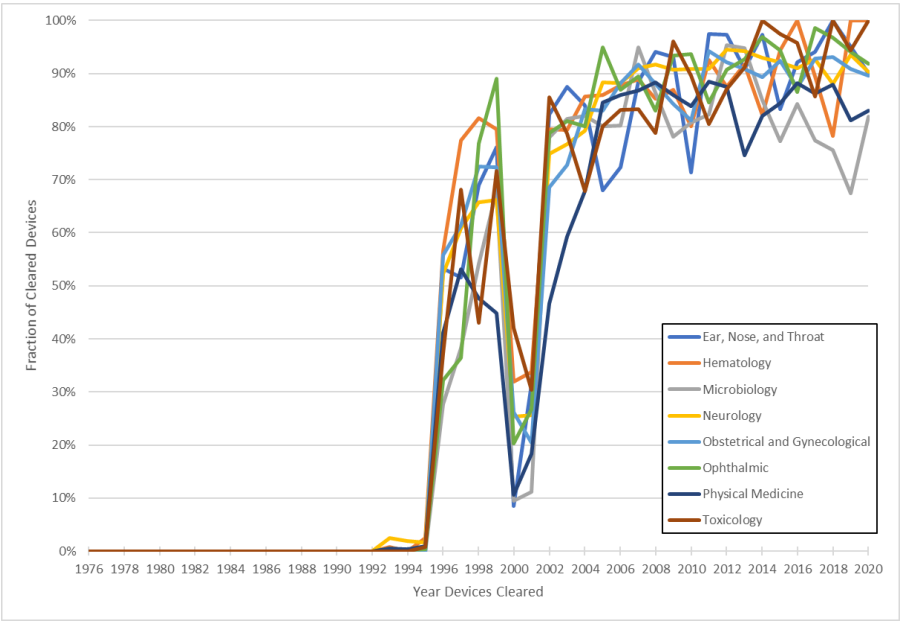
Mapping Process

The FDA's publicly available dataset on devices cleared under the 510(k) pathway includes detailed information on over 157,000 devices.[12] The chart below shows the total number of cleared devices by medical specialty between 1976 and 2020.



For some devices, predicate information is accessible through the FDA's searchable database of devices cleared under the 510(k) pathway.[13] Specifically, some device records include information on the device's predicate(s). However, as shown in the figure below, the documents are only available for a fraction of records. The records for devices cleared prior to 1996 rarely include documents and the records for devices cleared between 1999 and 2001 were comparatively less likely to include documents as well.





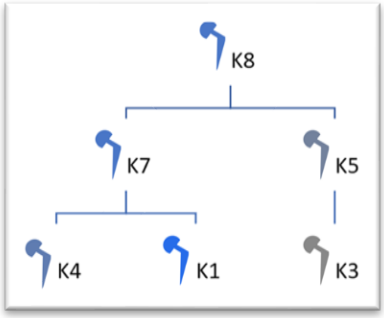
In general, the ability to precisely identify a device's predicate(s) declines the earlier a device was cleared. There are three primary reasons for this:

(1) the overall propensity that a record contains documents increases over time as gleaned from the salient trends in the charts above;
(2) the overall propensity for the documents to contain any information about the device's predicate(s) increases over time; and

(3) the propensity for the predicate information to be precise also increases over time. For instance, a document that vaguely refers to predicate(s) by tradename may refer to any number of devices and modifications of those devices that use the same trademark.

Predicate Chain

The lack of predicate information for devices cleared prior to 1996 creates significant barriers to fully mapping the series of devices that are linked through the 510(k) pathway. I refer to these series of links as the "predicate chain." As an example, suppose the following predicate chain for fictional hip replacement device K8:



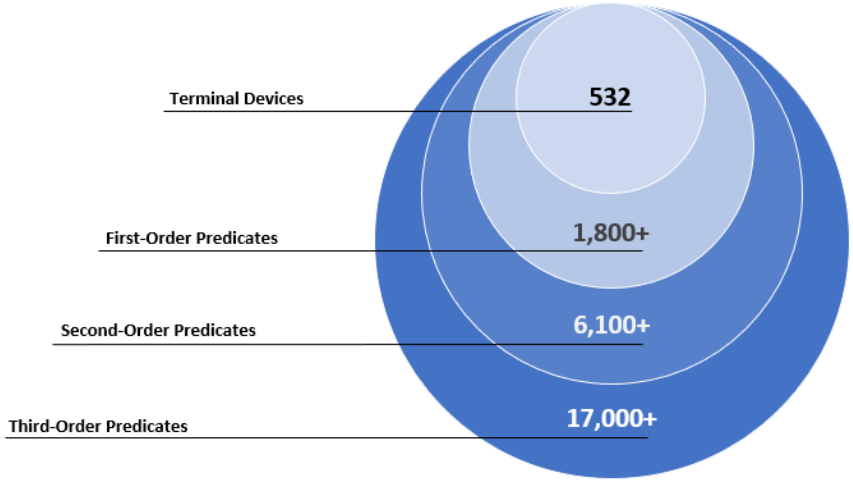
In this fictional example, device K8 claimed substantial equivalence to devices K7 and K5. In turn, device K7 claimed substantial equivalence to devices K4 and K1 while device K5 claimed substantial equivalence to device K3. The lack of predicate information for devices K1, K3 or K4 will restrict the ability to fully map the chain of devices that link not only to K1, K3 and K4, but also to devices K5, K7 and K8 which are part of the predicate chain of device K8. Nonetheless, mapping the predicate chain based on the predicate information that is available is highly informative.

Although the dataset includes information on over 157,000 devices cleared under the 510(k) pathway between 1976 and 2020, for the sake of both clarity and brevity, the remaining analysis will center on orthopedic devices cleared in 2020 for the following reasons:

- A starting point that is both recent and specific to a single year maximizes the propensity for accurate predicate information while also keeping the analysis in the context of devices recently cleared for the marketplace;
- More orthopedic devices were cleared between 1976 and 2020 than any other specialty with the exception of cardiovascular devices;
- Documents were more commonly available for orthopedic device records than any other specialty in all but two years;[14] and
- It is expected by many that demand for orthopedic devices will remain strong for the foreseeable future due to an increasing elderly population.

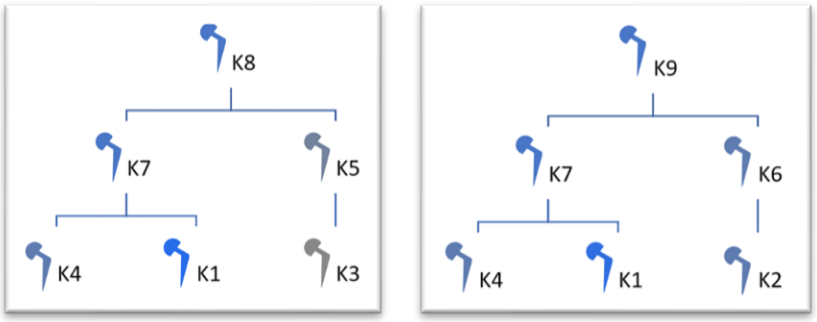
Orthopedic Predicate Chain

The analysis of the orthopedic predicate chain starts with the 532 orthopedic devices cleared under the 510(k) pathway in 2020 (hereafter referred to as the Terminal Devices) and maps the predicate chain for each of the 532 devices. The Terminal Devices claimed substantial equivalence to over 1,800 predicate devices (hereafter referred to as the First-Order Predicates). In turn, these First-Order Predicates claimed substantial equivalence to over 6,100 predicate devices (hereafter referred to as the Second-Order Predicates). In a third iteration, these Second-Order Predicates claimed substantial equivalence to over 17,000 predicate devices (hereafter referred to as the Third-Order Predicates).



While this analysis can be taken further (e.g., Fourth-Order Predicates), the above figure suffices to show that the number of devices in predicate chains can grow substantially when devices commonly have more than one predicate, as illustrated with orthopedic devices cleared in 2020.

The analysis thus far illustrates the magnitude of the predicate chain when the chain of each Terminal Device is examined separately. However, it is also enlightening to analyze the predicate chain for the Terminal Devices, not individually, but as a group. Multiple devices can claim substantial equivalence to the same predicate device. When examining the predicate chain as a group, one can identify the number of unique predicate devices at each link in the group's predicate chain rather than the aggregated number of predicates which may be present in multiple Terminal Device chains. For example, suppose the following predicate chains for fictional devices K8 and K9:



The two Terminal Devices (K8 and K9), as a group, claimed substantial equivalence to three *unique* First-Order Predicates (K7, K5, K6). In turn, these First-Order Predicates claimed substantial equivalence to four unique Second-Order Predicates (K4, K1, K3, K2). By contrast, when the predicate chains for the two Terminal Devices (K8 and K9) are examined individually, the overlap in the predicate chains leads to a higher number of First-Order and Second-Order Predicates.

Examination of the orthopedic predicate chain as a group reveals the potential for overlap in the predicate chains of Terminal Devices. The Terminal Devices claimed substantial equivalence to over 1,400 *unique* First-Order Predicates. In turn, the First-Order Predicates claimed substantial equivalence to over 2,700 unique Second-Order Predicates. Lastly, the Second-Order Predicates claimed substantial equivalence to over 3,400 unique Third-Order Predicates. A comparison of the number of unique predicates to the number of total predicates at each link in the chain reveals that there may be a substantial amount of overlap in the predicate chains of individual Terminal Devices. For example, there were over 17,000 Third-Order Predicates but these amounted to just over 3,400 unique devices. This suggests that, on average, a Third-Order device was used as the basis for substantial equivalence on approximately 5 instances.

This result raises several questions regarding the interconnectedness of medical devices and may further the concerns of critics of the 510(k) pathway. For example, suppose there is a device sans clinical testing that is of particular concern to these critics. If the device at issue is a predicate to multiple devices *along the same predicate chain* (i.e., shows up multiple times in the same predicate chain), critics of the 510(k) pathway may also have concern for additional devices in the chain, including the Terminal Device at the end of the chain. Alternatively, if the alarming device is a predicate to multiple devices *across several predicate chains*, critics may have concern for a wider set of devices. Regrettably, analyzing the degree of interconnectedness among medical devices, while intriguing, is a lengthy process that is best addressed in a separate article.

Breaking Down the Predicate Chain

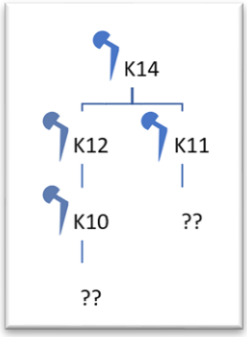
While the above analysis has been informative about the potential magnitude of the predicate chain, it is also advantageous to focus on the composition of the predicates. The early part of this article discussed the types of legally marketed devices on which equivalence was drawn (e.g., preamendment devices). Here we break down the composition of each link in the predicate chain based on these types:

- All First-Order Predicates were cleared through the 510(k) pathway;
- Less than 2 percent of Second-Order Predicates were approved through the PMA pathway. The rest of the Second-Order Predicates were cleared through the 510(k) pathway;
- Less than 1 percent of unique Third-Order Predicates were preamendment devices and less than 3 percent were approved through the PMA pathway. The rest of the Third-Order Predicates were cleared through the 510(k) pathway.

Perhaps unsurprisingly, these results indicate that the vast majority of devices within three links of the Terminal Device predicate chains were cleared through the 510(k) pathway while few of the devices are preamendments, approved through the PMA pathway then reclassified from Class III, and none were granted marketing authorization via the De Novo pathway.

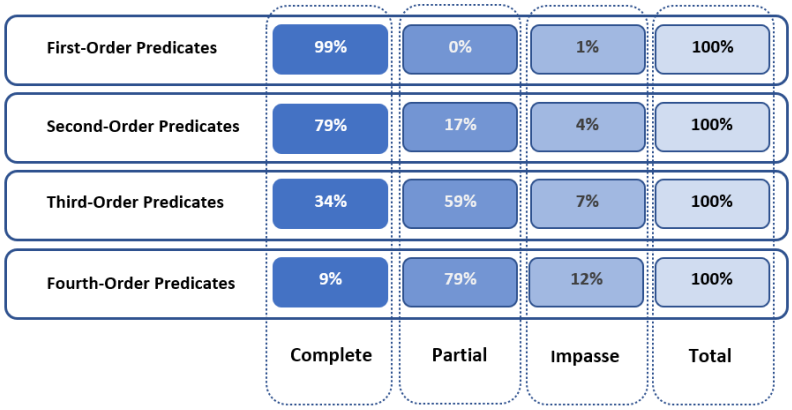
Linking Up to Terminal Devices

Until this point, the analysis has focused on the predicate information that is observable. However, as discussed earlier, incomplete predicate information can have a profound impact on the ability to fully map the predicate chain of Terminal Devices. For example, suppose the following predicate chain for fictional orthopedic device K14:



Device K14 has complete information on the First-Order Predicates to which substantial equivalence was claimed. However, K14 can only be partially mapped through the Second-Order Predicates because there is no information on the predicate(s) to device K11. Moreover, K14 cannot be mapped through the Third-Order Predicates because there is no information on the predicate(s) to device K10.

In the case of orthopedic devices, the impact of incomplete information is illustrated by the figure below which shows the fraction of Terminal Devices for which predicate information is both clearly identifiable and available for each order of the predicate chain.



Approximately 99 percent of Terminal Devices had information on the First-Order Predicates to which substantial equivalence was claimed while 1 percent of Terminal devices did not. However, the lack of predicate information impacts the ability to map the predicate chain at early stages in the chain.

- Approximately 79 percent of Terminal Devices can be completely mapped through Second-Order Predicates while 17 percent can only be partially mapped, and 4 percent of Terminal Devices have no Second-Order Predicate information;

- Approximately 34 percent of Terminal Devices can be completely mapped through Third-Order Predicates while 59 percent can only be partially mapped, and 7 percent of Terminal Devices have no Third-Order Predicate information; and
- Approximately 9 percent of Terminal Devices can be completely mapped through Fourth-Order Predicates while 79 percent can only be partially mapped, and 12 percent of Terminal Devices have no Fourth-Order Predicate information.

The above results indicate that the lack of predicate information quickly impairs the ability to fully map the predicate chains of Terminal Devices. Moreover, the analysis also suggests that the earlier tabulations on the total number of predicate devices, unique or otherwise, may significantly underestimate the true number of predicate devices.

Conclusion

A common criticism of the 510(k) pathway is that it can create so-called approval chains of devices that reach the marketplace without recent clinical testing. This article analyzes a uniquely assembled dataset that includes predicate information for many of the devices cleared between 1976 and 2020 to shed some light on this topic. However, lack of predicate information for many devices, particularly those cleared before 1996, limited the ability to fully map the series of devices that are linked through the 510(k) pathway, referred to as the predicate chain.

For the sake of both clarity and brevity, the analysis of predicate chains centered on orthopedic devices cleared in 2020 for a number of reasons that we have discussed in the article. In summary, here are the key takeaways from the analysis:

- The 532 orthopedic devices cleared in 2020 claimed substantial equivalence to over 1,800 predicates. Following the predicate chain an additional two links identified over 17,000 devices. The analysis sufficed to show that the number of devices in predicate chains can grow substantially when devices commonly have more than one predicate;
- Examination of the orthopedic predicate chain as a group reveals the potential for overlap in the predicate chains of Terminal Devices. A comparison of the number of unique predicates to the number of total predicates at each link in the chain shows that, on average, devices were used as the basis for substantial equivalence on multiple instances;
- The vast majority of devices within three links of the Terminal Device predicate chains were cleared through the 510(k) pathway; and
- The lack of predicate information impacts the ability to map the predicate chain at early stages in the chain. Less than 10 percent of orthopedic devices cleared in 2020 can be fully mapped through four links in the predicate chain.

[1] For more information on the transitive law of mathematics see “Transitive law,” Encyclopaedia Britannica, available at https://www.britannica.com/topic/logical-relation.

[2] “Overview of Device Regulation,” FDA, available at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation.

[3] For more information on what constitutes "substantial equivalence," refer to "Premarket Notification 510(k): What is Substantial Equivalence," FDA, available at https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k#se.

[4] "Premarket Notification 510(k)," FDA, available at https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k.

[5] "Premarket Notification 510(k)," FDA, available at https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k.

[6] Preamendment devices must have not significantly changed or been modified since May 28, 1976 and for which a regulation requiring Premarket Approval (PMA) has not been published by the FDA. "Premarket Notification 510(k)," FDA, available at https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k.

[7] "De Novo Classification Process (Evaluation of Automatic Class III Designation): Guidance for Industry and Food and Drug Administration Staff," U.S. Food and Drug Administration. October 30, 2017, p. 3, available at https://www.fda.gov/media/72674/download.

[8] "Biden Names Kessler Chief Science Officer for Covid Response," Wall Street Journal, January 15, 2021, available at https://www.wsj.com/articles/biden-names-kessler-chief-science-officer-for-covid-response-11610717005.

[9] "What the Netflix Documentary 'Bleeding Edge' Gets Right About the Dangers of Medical Devices in America," Time USA, LLC, July 27, 2018, available at https://time.com/5346330/what-the-netflix-documentary-bleeding-edge-gets-right-about-the-dangers-of-medical-devices-in-america/.

[10] "Downloadable 510(k) Files," FDA, available at https://www.fda.gov/medical-devices/510k-clearances/downloadable-510k-files; "Download Product Code Classification Files," FDA, available at https://www.fda.gov/medical-devices/classify-your-medical-device/download-product-code-classification-files.

[11] In most instances, the identifying predicate information was the predicate's 510(k) number. However in some instances the predicate's name was the only identifying information available. In these latter instances, the same FDA database was used to search for the 510(k) numbers using the predicate's name.

[12] The FDA's data may not include information for all devices that were once cleared for issues such as "administrative or IT matters" per email correspondence with 510K_Program@fda.hhs.gov dated April 5, 2021.

[13] "510(k) Premarket Notification: Search Database," FDA, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm.

[14] Documents were available for 4 percent of hematology devices and 2 percent of orthopedic devices cleared in 1995. Documents were available for 42 percent of toxicology devices and 38 percent of orthopedic devices cleared in 2000.

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Dr. Omar Robles is Managing Partner at Emerging Health LLC. He has worked on numerous cases in the area of commercial litigation, antitrust claims, intellectual property, and commercial damages. Dr. Robles has analyzed economic issues in a range of industries with extensive experience in the life sciences industry. Dr. Robles has consulted on cases concerning medical devices, over-the-counter pharmaceuticals, and dietary supplements. In addition, He has worked with prescription pharmaceuticals in multiple therapeutic classes sold in the US, Canada, and Latin America. His engagements have concerned matters litigated in US District Courts, State Courts, Canadian courts, Patent Trial and Appeal Board proceedings, and Arbitration.

Dr. Robles has also evaluated antitrust claims and damages in relation to false advertising, monopolization claims, antitrust counterclaims to patent cases, alleged reverse payments, and product hops. In the area of intellectual property, Dr. Robles has provided economic analysis on issues associated with commercial success, patent infringement, irreparable harm, and valuation.

In addition to publishing economics articles in top economic journals, Dr. Robles is a Lecturer at the University of California-Berkeley School of Public Health regarding regulatory science and drug development. He has previously taught at Harvard University, Georgetown University, and the University of Maryland. Dr. Robles is the proud recipient of Harvard's prestigious Joseph R. Levenson Memorial Teaching Prize for Excellence in Undergraduate Teaching from the Undergraduate Council.