Supplemental Online Content

Kadakia KT, Dhruva SS, Caraballo C, Ross JS, Krumholz HM. Use of recalled devices in new device authorizations under the US Food and Drug Administration's 510(k) pathway and risk of subsequent recalls. *JAMA*. doi:10.1001/jama.2022.23279

This supplemental material has been provided by the authors to give readers additional information about their work.

SUPPLEMENTARY APPENDIX

eMethods

Sample Construction

The FDA publishes a list of all Class I medical recalls, by year, on its website.[1] While the majority of devices subject to Class I recalls are devices cleared under 510(k), the listing may also include devices authorized under other regulatory pathways, including Premarket Approval (PMA), De Novo, and Emergency Use Authorizations (which was applicable for some devices in the 2020 and 2021 listings due to the COVID-19 pandemic). These listings summarize information about the recalled product, the intended use of the device, and the reason for recall. The listing also includes links to the FDA's Medical Device Recalls Database, which includes entries for all device recalls, not just Class I. Entries in the database are categorized by a unique recall number and event ID, and include the device number (e.g., 510(k) number, PMA number) and by a variable number of other relevant identifiers (e.g., lot number, serial number, unique device identifiers).

When constructing our sample, we sought to account for potential duplications. Duplications could arise in one of two ways.

First, some devices were repeated across multiple listings in the FDA's annual log of Class I recalls. This was because most device recalls occur voluntarily by the manufacturer, and some devices may be produced by multiple manufacturers. We resolved these situations by checking the Medical Device Recalls Database for the 510(k) number of the device, and only counting the device once in our sample. For example, four different listings were posted for the Alaris Infusion Pumps, Model 8100, as the device has multiple manufacturers (BioMedical Equipment Service Co, Infusion Pump Repair, The Biomed Guys, Step-Har Medical LLC).[2-5] However, each listing referred to the same 510(k) number (K133532) and was therefore considered duplicative.

Second, some listings included links to multiple entries in the FDA's Medical Device Recalls Database. These repeats could stem from the fact that recalls might have affected specific lots or versions of the device. We also resolved these situations by confirming the 510(k) number of the device and excluding duplicates from the final count. For example, the FDA's webpage for the Class I recall of the Arrow AutoCAT®2 and AC3 Optimus® IABP Series Due to Possible Breakdown of Motor Connector Wires ("Arrow") includes links to 10 different recall database entries that referred back to two different 510(k) numbers (K060309 and K162820), which were ultimately selected for inclusion in our sample.[6]

Repeats Within Predicate Lineages

As we traced predicate lineages for each index device, we observed several instances in which several index devices were authorized using the same predicate, and in which several descendant devices were authorized using the same index device as a predicate. Accordingly, we accounted for these duplicates across both predicates (14 examples) and descendants (15 examples) in our calculations of summary statistics.

For predicates, consider the following example. Three index devices—the Respironics BiPAP C Series (K102465), BiPAP Ventilator Series Oximetry (K111378), and Respironics BiPAP A30

Ventilatory Support System (K113053)—all cited the Respironics BiPAP AVAPS Ventilatory Support System (K092818) as a predicate device.[7-9]

For descendants, consider the following example. The Genesis Medical Interventional F.A.S.T. System. (K040010) listed two different index devices—the Over The Wire Embolectomy Catheter, Model 2302 (K022145) and the Latis Graft Cleaning Catheter (K973465)—as predicates for substantial equivalence determinations.[10]

Validation of Basil Systems Platform

The Basil Systems platform uses a proprietary artificial intelligence platform to conduct textual analyses of regulatory documents stored in the FDA's database. If name or number of a device is contained in a document stored in an FDA database (e.g., the 510(k) database, the recalls database), then a query using that name or number as the search term in Basil Systems will yield a result.

Because the Devices@FDA database does not have the function of mapping relationships between devices and their predicates, we used the Basil Systems platform to identify potential associations across predicate lineages. The platform provides a map identifying the predicate, reference, and descendant device(s) for an index device. We searched the 510(k) number for each index device in the platform to generate predicate lineages for (1) for the index devices in our sample, (2) predicates subject to Class I recalls, and (3) recall-free controls matched to predicates subject to Class I recalls, We then validated that the associations generated by Basil Systems were legitimate by searching the Devices@FDA database to identify the decision memo for the descendant device and confirm that the index device listed in Basil Systems was indeed the predicate for the descendant. The table below documents the number of raw associations and validated associations for each of the three cohorts that we constructed predicate lineages for using Basil Systems.

Predicate Lineage Validation				
Device Cohort	*Number of Devices in Cohort*	*Number of Descendants Identified Using Basil Systems*	*Number of Validated Descendants*	*Validation Rate*[b]
Index Devices	104[c]	350	265	75.7%
Predicates Subject to Class I Recalls	64	221	177	80.1%
Matched Controls for Predicates	64	132	121	91.7%

[a] This does not account for the number of unique descendants. The uniqueness of the descendants does not matter for the purposes of the validation, as Basil Systems is identifying relationships between an individual predicate and descendant, and a descendant could be repeated across multiple predicates and still require independent validation each time. For example, Device A could have 2 descendants (Device B and Device C) and Device D could have two descendants (Device C and Device E). Therefore, across the 4 descendant relationships generated by Basil Systems, only 3 are unique (as Device C is repeated across the predicate lineages for both Device A and Device D). However, each of these descendant relationships has to be validated independently, hence why "uniqueness" does not matter for the purpose of this validation analysis.
[b] Validation rate is the number of "true" associations reported in Basil based on a manual review of a device's regulatory filings (see below for further discussion on examples for predicate relationships that were not validated).
[c] Of the 156 index devices, only 104 had predicate lineages (showing descendants) in Basil.

The instances in which the text-based association in the Basil Systems platform was not specifically a predicate-device relationship typically fell into three categories:

- *Predicate versus reference device:* In some cases, the index device was listed as a "reference" device, but not a "predicate" device. Reference devices are devices that can

same product code and regulation specialty. We confirmed that K001686 had never been subject to a recall of any class, had a different manufacturer from the index device, did not use a predicate that was included in the study sample (as this would introduce bias into the association), and did have a predicate lineage in Basil Systems (to enable comparison of recalls across descendants).[15] We reconstructed the predicate lineage for K001686 using Basil Systems, identifying five devices (K021573, K022679, K022132, K040574, K052863), of which one was not validated (K040574; did not identify the control as a predicate in the decision letter). Having validated the descendants for the control, we then determined the recall history of each control descendant, and used this information for the risk ratio calculation.

While this approach could be followed for most of the matched controls, there were a few scenarios in which adjustments were required because of the limited number of potential control devices. In general, if a device did not meet eligibility as a control, we proceeded to use the device that was next closest in authorization date. Examples of these scenarios include the following:

Scenario #1: the closest control device had a recall. For example, for predicate device K133801 (authorized May 7, 2014), the closest devices with the same product code (FRN) was K141102. However, this device was ineligible to be a control because it had been subject to recalls. Therefore, we identified the next closest device authorized under this product code that met all other matching criteria (K140783, authorized October 17, 2014) and used it as the matched control.

Scenario #2: devices had the same manufacturer. Medical device markets have some degree of consolidation because some manufacturers focus in specific product areas. This is especially important to consider in 510(k), as a single manufacturer could make dozens of devices within the same lineage over an extended period. Therefore, we sought to ensure that the manufacturer of the index device and the control device were different. For example, the closest possible match for K990172 was K990352, but both devices had the same manufacturer (Coulter Corp.). Therefore, we selected the next available match with a different manufacturer; in this case, K990311, manufactured by ABX Diagnostics.

Scenario #3: devices could not be matched based on product code. Product code is the most specific way to match devices because it indicates that devices are not only the same specialty (e.g., cardiovascular) and therefore reviewed by the same personnel at FDA, but also that the function of the devices is also similar (e.g., catheters, stents, etc.). However, in some cases, it was not possible to match based on product code alone if all available matches had the same manufacturer. For example, for K052549—a blood lead diagnostic test—was cleared under product code DOF. However, all devices cleared between 1997 and 2015 under this product code were manufactured by the same company (Magellan, previously known as ESA), and many of the devices cite one another as predicates. Therefore, it would be inappropriate to attempt to use these as controls. Instead, we sought to match based on the next level of regulatory similarity: medical specialty. In this case, we identified a device cleared in the same time period (September 12, 2005, only 3 weeks prior to the predicate's clearance on October 6, 2005) under the same specialty (Toxicology) and used it (K052015) as the matched control.

be "used to support scientific methodology or standard reference values" but are not used for the purposes of determining substantial equivalence under 510(k).[11] For example, while Basil Systems identified K152068 as a potential descendant of K093416, we excluded it from our analysis as the K093416 decision memo listed K152068 as a reference device, not a predicate.[12]

- *Predicate versus device component:* Some devices have several constituent parts, each of which may be covered under a different 510(k) authorization. In some cases, index devices were listed in the decision memo of a potential descendant device as an example of a relevant component (e.g., "compatible module," "host system"). For example, while Basil Systems identified K150298 as a descendant of K133576, we excluded K150298 from our analysis as the decision memo listed K133576 as a compatible host system for the device, but not an actual predicate.[13]
- *Mistakes in the FDA decision memo:* In some cases, the FDA decision memos themselves contained errors, which were detected by the Basil Systems platform as a potential predicate-device relationship. For example, Basil Systems identified K191729 as a potential descendant of K111386. This association is illogical, as K191729 is an influenza test and K111386 is a syringe infusion pump, and indeed, the predicate listed in the decision memo of K191729 is K111387 (a one-digit difference). However, on page 8 of the decision memo for K191729, there is an error that describes the device as "substantially equivalent to the predicate device, as originally cleared through K111386." For this reason, K191729 was excluded from our analysis of descendants.[14]

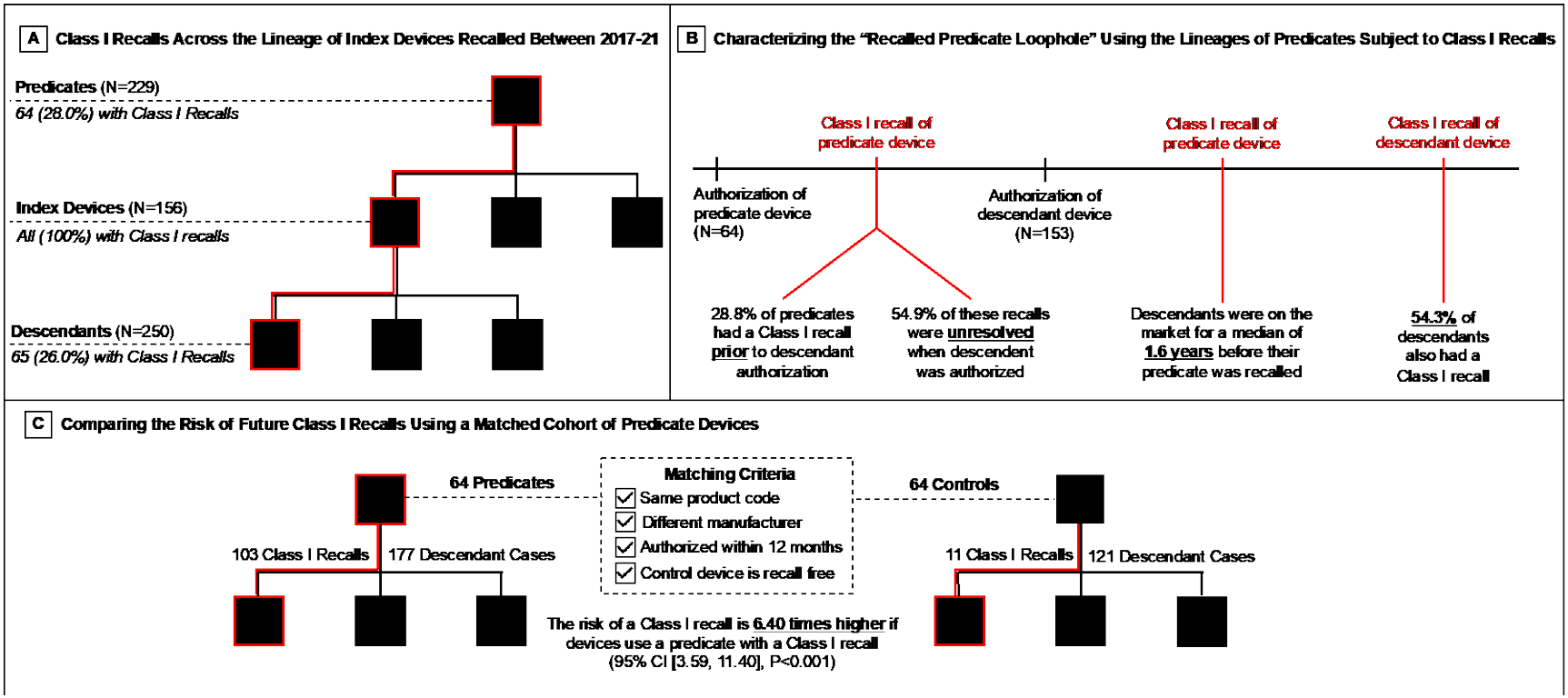
It is possible that there may be additional descendant devices that were not captured by the Basil Systems platform; however, the majority of index-descendant relationships were likely identified given that the platform relies on text-based analysis of regulatory filings. Any missing associations would therefore reflect a lack of public reporting, and would consequently not be identifiable using any platform if a digital record of a decision memo containing the 510(k) number and predicate number was not available.

Matched Cohort Analysis

We matched devices to predicate devices based on authorization date and product code, while controlling for manufacturer, any shared predicates, and history of prior recall. We also had to ensure that the control device had a predicate lineage in Basil Systems (as if there was no predicate lineage, there would be no descendants to evaluate as part of the risk ratio calculation for future risk of recall).

As an example of this matching methodology, consider the following. K992133 was used as the predicate for the index device K083526, and was subject to a Class I recall. The device was manufactured by Newport Medical Instruments, Inc. and authorized on August 4, 2000 under the product code CBK, which encompasses devices that are "Ventilator, Continuous, Facility Use" under the Anesthesiology regulation medical specialty and review panel. To identify a matched control, we searched the Devices@FDA database for all 510(k) devices authorized within 12 months of August 4, 2008 under the product code CBK. The device with the closest date of authorization to the predicate was K001686, which was manufactured by Hamilton Medical, Inc. and authorized by FDA on June 23, 2000 (so two months prior to the matched case) under the

eFigure 1. Use and Consequences of Using Recalled Predicates in the 510(k) Pathway



eTable 1: Recall Rates Among Unique Descendant Devices	
Predicates	
Total number of unique devices authorized using predicates	153
Number of unique devices subject to recalls of any class	100 (65.4%)
Number of unique devices subject to Class I recalls	83 (54.3%)
Index Devices	
Number of unique devices authorized using index devices	250
Number of unique descendants subject to recalls of any class	101 (40.4%)
Number of unique descendants subject to Class I recalls	65 (26.0%)

eTable 2: Risk Ratios for Unique Descendant Devices[a]		
Characteristics	**Cases (Predicates with Class I Recalls)**	**Matched Controls**
Study population		
Sample size – total no.	64	64
Descendant devices		
Sample size – unique no.	153	116
Number of descendant devices with recalls of any class – no. (%) Number of descendant devices with Class I recalls – no. (%)	100 (65.4%) 83 (54.3%)	21 (18.1%) 8 (6.9%)
Statistical analyses		
Risk of device recall of any class if authorized using a predicate subject to a Class I recall – RR (95% CI) Risk of Class I device recall if authorized using a predicate subject to a Class I recall – RR (95% CI)	3.61 (2.41, 5.41), $P<0.001$ 7.87 (3.97, 15.59), $P<0.001$	

[a] Risk ratios were recalculated using only the unique number of descendant devices.

eReferences

1. U.S. Food and Drug Administration. Medical device recalls. August 9, 2021. https://www.fda.gov/medical-devices/medical-device-safety/medical-device-recalls. Accessed June 1, 2022.

2. U.S. Food and Drug Administration. Bio-Medical Equipment Service Co. recalls Alaris Infusion Pump Module 8100 Bezel due to possible cracked or separated bezel repair posts. August 24, 2021. https://www.fda.gov/medical-devices/medical-device-recalls/bio-medical-equipment-service-co-recalls-alaris-infusion-pump-module-8100-bezel-due-possible-cracked. Accessed June 1, 2022.

3. U.S. Food and Drug Administration. Infusion Pump Repair recalls Alaris Infusion Pump Module 8100 Bezel due to possible cracked or separated bezel repair posts. June 16, 2021. https://www.fda.gov/medical-devices/medical-device-recalls/infusion-pump-repair-recalls-alaris-infusion-pump-module-8100-bezel-due-possible-cracked-or. Accessed June 1, 2022.

4. U.S. Food and Drug Administration. The Biomed Guys recalls Alaris Infusion Pump Module 8100 Bezel due to possible cracked or separated bezel repair posts. June 2, 2021. https://www.fda.gov/medical-devices/medical-device-recalls/biomed-guys-recalls-alaris-infusion-pump-module-8100-bezel-due-possible-cracked-or-separated-bezel. Accessed June 1, 2022.

5. U.S. Food and Drug Administration. Step-Har Medical recalls Alaris Infusion Pump Module 8100 Bezel due to possible cracked or separated bezel repair posts. May 28, 2021. https://www.fda.gov/medical-devices/medical-device-recalls/step-har-medical-recalls-alaris-infusion-pump-module-8100-bezel-due-possible-cracked-or-separated. Accessed June 1, 2022.

6. U.S. Food and Drug Administration. Arrow International Inc. recalls Arrow AutoCAT®2 and AC3 Optimus® IABP Series due to possible breakdown of motor connector wires. July 2, 2022. https://www.fda.gov/medical-devices/medical-device-recalls/arrow-international-inc-recalls-arrow-autocatr2-and-ac3-optimusr-iabp-series-due-possible-breakdown. Accessed June 1, 2022.

7. U.S. Food and Drug Administration. 510(k) premarket notification: K102465. May 9, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K102465. Accessed June 1, 2022.

8. U.S. Food and Drug Administration. 510(k) premarket notification: K111378. May 9, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K111378. Accessed June 1, 2022.

9. U.S. Food and Drug Administration. 510(k) premarket notification: K113053. May 9, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K113053. Accessed June 1, 2022.

10. U.S. Food and Drug Administration. 510(k) premarket notification: K040010. May 9, 2022. https://www.accessdata.fda.gov/scrIpts/cdrh/cfdocs/cfpmn/pmn.cfm?id=K040010. June 1, 2022.

11. U.S. Food and Drug Administration. The 510(k) program – transcript. January 4, 2018. https://www.fda.gov/training-and-continuing-education/cdrh-learn/510k-program-transcript. Accessed June 1, 2022.

12. U.S. Food and Drug Administration. 510(k) premarket notification: K093416. November 21, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K093416. Accessed November 23, 2022.

13. U.S. Food and Drug Administration. 510(k) premarket notification: K150298. November 21, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K150298. Accessed November 23, 2022.

14. U.S. Food and Drug Administration. 510(k) premarket notification: K191729. November 21, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?id=K191729. Accessed November 23, 2022.

15. U.S. Food and Drug Administration. 510(k) premarket notification: K001686. November 21, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K001686. Accessed November 23, 2022.