



## The 510(k) Ancestry of a Metal-on-Metal Hip Implant

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Many medical devices that pose great safety risks to Americans, including metal-on-metal hip implants, currently enter the U.S. market through a Food and Drug Administration (FDA) regulatory

pathway that is not intended for evaluating safety and effectiveness. This pathway, called the 510(k) process, instead involves evaluation of “substantial equivalence” to previously cleared devices, many of which have never been assessed for safety and effectiveness and some of which are no longer in use because of poor clinical performance.

The Medical Device Amendments of 1976 created three classes of devices: class I included low-risk devices, such as toothbrushes; class II contained moderate-risk devices, such as infusion pumps; and class III included high-risk devices and those awaiting proper classification, such as metal-on-metal hip implants. These classes roughly

corresponded to the level of premarketing review required. Thus, class I and II devices underwent review for substantial equivalence to devices already on the market, also called preamendment devices (although subsequent legislation granted exemptions). Class III devices were meant to undergo the more rigorous premarket approval (PMA), the only pathway that requires clinical data. However, class III devices were allowed to receive review for substantial equivalence temporarily, until the FDA down-classified these devices or promulgated regulations requiring PMA. Congress had always intended class III devices to undergo PMA, and in 1990, it directed the agency to

establish a schedule to finish the transition to PMAs for all devices that were to remain in class III.<sup>1</sup>

As of December 19, 2012, however, the FDA still had not completed this transition to PMA for high-risk devices, although it had stated its intention to clear proposed rules for all remaining class III preamendment devices by December 31, 2012.<sup>2</sup> Currently, 19 different types of class III devices, including metal-on-metal hip implants, are allowed to reach patients through 510(k) clearance. Because of this loophole, companies that market these devices are often legally able to obtain clearance without demonstrating safety and effectiveness through clinical studies, but by claiming substantial equivalence to earlier “predicate devices” — or pieces of those devices — which may also have been found substantially equivalent to even earlier devices, and so on, all the way back to preamendment devices. Be-

cause many predicates have never been assessed for safety and effectiveness, an FDA finding of substantial equivalence does not mean that a new device is safe and effective; it means only that the device is deemed no less safe and no less effective than a predicate.<sup>1</sup> Even voluntarily recalled devices



An interactive graphic is available at NEJM.org

can serve as predicates, as long as the FDA did not formally remove these devices from the mar-

ket or a court did not find them adulterated or misbranded.<sup>1</sup>

One prominent type of class III device that remains eligible for 510(k) clearance is metal-on-metal hip implants, such as the DePuy ASR XL Acetabular Cup System, which received FDA clearance in July 2008 without a clinical study. The Australian Orthopaedic Association National Joint Replacement Registry initially reported in September 2008 that this device required revision surgery at a high rate, and in 2010 the National Joint Registry (NJR) for England and Wales reported a 5-year revision rate of approximately 13%, which was more

Using FDA documents obtained from the agency's database and Freedom of Information Office, we traced the ancestry of the ASR XL back more than five decades, through a total of 95 different devices (including femoral stems), including 15 different femoral heads and sleeves and 52 different acetabular components (see figure, and the interactive graphic, available with the full text of this article at NEJM.org).

The 510(k) clearance for the ASR XL focused on three characteristics: the porous bone ingrowth surface, metal-on-metal articulation, and large femoral head sizes (57 to 63 mm), which were larger than those of the predicate total hip prostheses. These three characteristics were uniquely combined in the ASR XL but were evaluated for "substantial equivalence" by comparing select characteristics to different predicate devices, none of which contained all of these characteristics (i.e., they were "split predicates").

The porous bone ingrowth surface was not specific to the type of articulation; thus, in most cases, the predicates were not

icates, some of which differed substantially in design from the ASR XL or had poor clinical performance. Ultimately, clearance was based on the claim that these predicate devices were substantially equivalent to three prostheses that were used before 1976: the McKee-Farrar, Ring, and Sivash metal-on-metal total hip prostheses. It is important to note that these three devices were discontinued long ago (and well before clearance of the ASR XL) because their risk of revision was so much higher than that of other hip prostheses.<sup>3,4</sup>

One metal-on-metal hip in use at the time of the application and whose use was well supported by clinical evidence was the original Metasul hip. However, this hip differed substantially in design from the ASR XL in two major ways. The cup was not solid metal, but instead consisted of a metal shell and a metal articular surface inlay with a polyethylene "sandwich" between the two. A second difference was head size: the Metasul had much smaller heads ( $\leq 32$  mm) than the ASR XL.

The use of larger heads was an important characteristic of the ASR XL. The clearance for the large metal heads with sleeves was based in part on predicates that were not used in total hip replacement but were designed for use in *partial* hip replacement, in which the large metal heads articulate with the natural articular cartilage of the acetabulum, not with a metal cup.

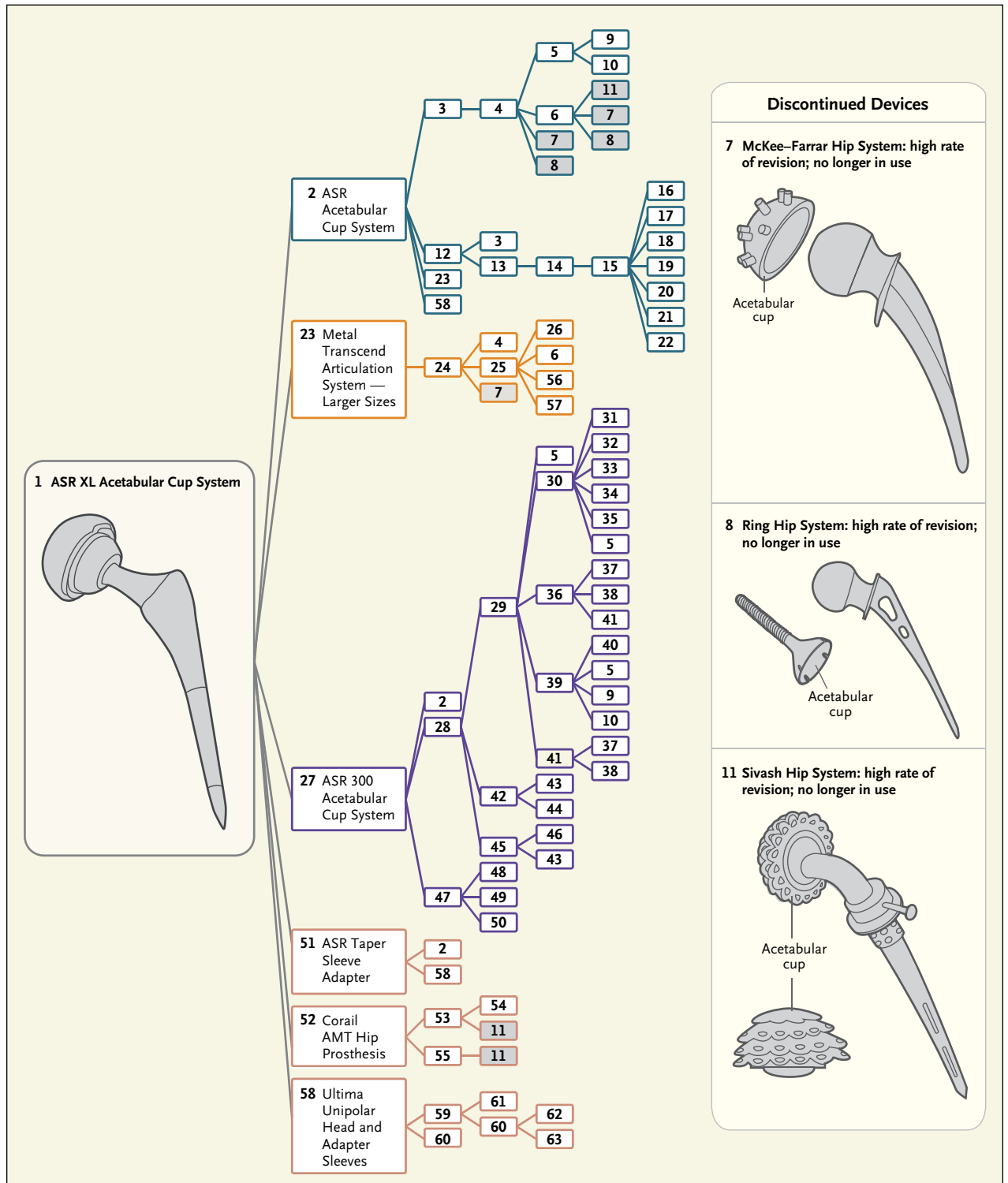
This ancestry reveals serious flaws in the 510(k) procedure for metal-on-metal hips, which resulted in clearance of a new device that was never shown to be safe and effective. A clinical trial might have identified the high

***This ancestry reveals serious flaws in the 510(k) procedure for metal-on-metal hips, which resulted in clearance of a new device that was never shown to be safe and effective.***

than four times the registry's reported 5-year revision rate for all hip-replacement prostheses combined. DePuy voluntarily recalled the ASR XL in Australia in 2009, citing "declining demand" as a reason, and then worldwide in 2010 because of the high revision rate reported by the NJR.

metal-on-metal and were substantially different in design from the ASR XL. None of the predicates in the ancestry had the same combination of characteristics as the ASR XL acetabular component.

Clearance of the large metal-on-metal articulation was based on a much smaller group of pred-



The 510(k) Ancestry of the DePuy ASR XL Femoral Heads, Sleeves, and Acetabular Components.

Each number represents a corresponding number in the Supplementary Appendix (available at NEJM.org), where the device names, companies, 510(k) numbers, and decision dates for most devices can be found.

revision rate of the ASR, which became evident after 9 months when it was compared with all other total conventional hip prostheses in the Australian Joint Registry (9-month-to-1-year hazard ratio, adjusted for age and sex, 2.62 [95% confidence interval, 1.67 to 4.11]) and which precipitously worsened over time.<sup>5</sup>

As thousands of Americans are painfully learning, there are unknown risks with devices that enter the market without clinical data showing safety and effectiveness, and implanted body parts cannot be recalled as easily as defective auto parts. The recently passed Medical Device User Fee and Modernization Act contains a provision that should make it

easier for the FDA to close the loophole for the remaining 19 class III devices by allowing the agency to reclassify devices by order rather than through regulation. There would be value in an FDA-sanctioned registry.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## Post-Hospital Syndrome — An Acquired, Transient Condition of Generalized Risk

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To promote successful recovery after a hospitalization, health care professionals often focus on issues related to the acute illness that precipitated the hospitalization. Their disproportionate attention to the hospitalization's cause, however, may be misdirected. Patients who were recently hospitalized are not only recovering from their acute illness; they also experience a period of generalized risk for a range of adverse health events. Thus, their condition may be better characterized as a post-hospital syndrome, an acquired, transient period of vulnerability. This theory would suggest that the risks in the critical 30-day period after discharge might derive as much from the allostatic and physiological stress that patients experience

in the hospital as they do from the lingering effects of the original acute illness. At the time of discharge, physiological systems are impaired, reserves are depleted, and the body cannot effectively defend against health threats.

Nearly one fifth of Medicare patients discharged from a hospital — approximately 2.6 million seniors — have an acute medical problem within the subsequent 30 days that necessitates another hospitalization. These recently discharged patients have heightened risks of myriad conditions, many of which appear to have little in common with the initial diagnosis. For example, among patients admitted for treatment of heart failure, pneumonia, or chronic obstructive pulmonary disease

(COPD), the cause of readmission is the same as that of the index admission for only 37%, 29%, and 36%, respectively.<sup>1</sup> The causes of readmission, regardless of the original admitting diagnosis, commonly include heart failure, pneumonia, COPD, infection, gastrointestinal conditions, mental illness, metabolic derangements, and trauma (see graph). The breadth of these readmission diagnoses has been shown in studies using administrative claims and those using chart reviews. Thus, this observation is not likely to be merely the result of variation in coding. Further evidence of the distinctiveness of this syndrome is that information about the severity of the original acute illness predicts poorly which patients will have an adverse medi-