Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death among men and women combined in the USA. In 2010, the national cost of cancer care was estimated to be US$124.57 billion, with CRC accounting for US$14.14 billion. If current trends continue, the cost of CRC care could rise to US$17.7 billion by the year 2020 [2]. The value of CRC screening is well recognized [3]. The 5-year survival for CRC is approximately 65%, but survival can substantially improve if cancer is detected early, while localized and amenable to complete surgical excision; 5-year relative survival is 90% for patients with localized disease compared with 13% for those with distant CRC [1]. Screening in asymptomatic patients is thus of vital importance, as it can detect polyps before they become cancerous, or can catch CRC in early localized stages when treatment is the most effective [4]. Multiple screening options are available including colonoscopy, the currently most comprehensive and accurate option, flexible sigmoidoscopy, fecal occult blood tests and fecal immunochemical test (FIT). Despite the availability of these options, screening rates remain suboptimal [4–6]. Cologuard® (Exact Sciences Corporation, Madison, WI, USA) is a non-invasive CRC screening test that entered the US market in 2014 and is the first molecular diagnostic product approved through a pilot parallel review program with the FDA–Centers for Medicare & Medicaid Services (FDA-CMS), a process introduced to streamline the regulatory and reimbursement pathways for innovative products. In this report, we aim to describe the science behind the Cologuard test, Exact Sciences’ experience with the parallel review pathway and the potential implications for the future of diagnostic development and commercialization.
human DNA. In contrast, CRC cells, and to a lesser extent pre-cancerous lesions, shed altered DNA into the stool. The biomarkers consist of specific altered DNA fragments from several genes which can be detected by selective DNA amplification techniques employed by Cologuard. Cancers and pre cancers may also bleed releasing hemoglobin in the stool. Cologuard is designed to detect 11 different DNA markers including two methylated genes, seven DNA mutations and hemoglobin. When the levels of these biomarkers exceed established thresholds optimized for the detection of CRC, the test is ’Positive’ [7].

The specific biomarkers assessed include N-myc downstream regulated gene 4 (NDRG4) and the bone morphogenetic protein 3 (BMP3), both of which have been shown to be hypermethylated in CRC [89]. In addition, seven mutations in exon 2 of v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) are included, which account for 98% of KRAS mutations in CRC [10]. Both methylated DNA and KRAS mutations have been shown to be present in the stool of patients with CRC and precancersous lesions [10,11], which means that Cologuard can detect premalignant lesions at early onset of abnormality as well as both early- and late-stage cancers [7]. Results from the methylation, mutation and hemoglobin assays are then combined to provide a single qualitative result for clinical use – ‘positive’ or ‘negative’ [7]. A positive result means the test detected levels of abnormal DNA and/or blood that could be the result of a cancerous or precancerous lesion in the colon, and the patient should be referred for a diagnostic colonoscopy [7]. A negative result means that elevated levels of abnormal DNA or blood were not detected, so patients can continue with a regular screening schedule [7]. Cologuard includes β-actin advanced precancerous lesions. When compared with colonoscopy as the reference standard, Cologuard demonstrated a sensitivity of 92.3% and a specificity of 86.6% for detection of CRC [7,13]. The sensitivity of Cologuard was found to be significantly higher than that of FIT for detection of both CRC (92.3 vs 73.8%, respectively; p = 0.002) and advanced precancerous lesions (42.4 vs 23.8%, respectively; p < 0.001) (Figure 1). Specificities were 86.6 and 94.9% for Cologuard and FIT, respectively, among participants with non-advanced or negative findings (p < 0.001) and 89.8 and 96.4%, respectively, among those with negative results on colonoscopy (p < 0.001). Cologuard detected 69.2% of advanced pre-cancerous lesions with high-grade dysplasia versus 46.2% with FIT (p = 0.004) [12].

**FDA premarket approval for high-risk in vitro diagnostics**

The pathway to patient access for any medical device or diagnostic starts with the submission of an application to the FDA for review of the clinical safety and effectiveness of the product. The FDA has defined three categories of diagnostic devices for evaluation: analyte specific reagents, laboratory developed tests and in vitro diagnostics (IVDs) [14,15]. IVDs are further classified into class I, II and III products according to the level of risk and the regulatory control needed to assure safety and efficacy (Table 1) [16,17]. High-risk IVDs (class III) are those products that support or sustain human life, are of substantial importance in preventing impairment of human health or present a potential, unreasonable risk of illness or injury [18]. Accordingly, the FDA reviews innovative, class III IVDs under the premarket approval (PMA) process (Figure 2) [18]. Cologuard
was deemed a class III product and therefore a PMA application was required. PMA is the most stringent device application required by the FDA and requires the highest burden of scientific data for approval. PMA development can be a lengthy process, requiring significant clinical and analytical validation of the assay. The average review time from final submission of the PMA to FDA approval was 355 days in 2013 (based on incomplete cohort data; 8 of 29 PMAs) [19].

**The CMS National Coverage Determination pathway**

Following FDA marketing approval (or clearance), the manufacturer must seek reimbursement and coverage from public and private payers, who decide if the technology’s scientific evidence meets their coverage criteria and who dictate the payment level. The criteria that some payers use to approve new technologies are shown in Table 2 [20]. The determination of whether or not a specific product meets the ‘reasonable and necessary’ threshold for reimbursement coverage under Medicare, the largest payer in the USA, falls under the sole responsibility of CMS [21]. CMS can issue a coverage policy at the national level in the form of a National Coverage Determination (NCD), which is binding for all Medicare organizations, or the policy can be determined at the local level by individual regional Medicare administrative contractors [22].

<table>
<thead>
<tr>
<th>Type of in vitro diagnostic</th>
<th>Risk</th>
<th>Description</th>
<th>Application</th>
<th>Target review time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Low to moderate</td>
<td>Devices subject to general controls</td>
<td>Exempt</td>
<td>Registration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Some may require 510(k) submissions</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>Moderate to high</td>
<td>Devices subject to general and special controls</td>
<td>510 (k)</td>
<td>90 days</td>
</tr>
<tr>
<td>Class III</td>
<td>High</td>
<td>Devices subject to general and special controls, and premarket clearance</td>
<td>Premarket approval</td>
<td>180 days</td>
</tr>
</tbody>
</table>

**Figure 2. The FDA-CMS parallel review pathway potentially shortens the review time for diagnostic products [21,24].**

CMS: Centers for Medicare & Medicaid Services; NCD: National Coverage Determination; PMA: Premarket approval.

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*Table 1. In vitro diagnostic categories* [16,17].
cesses can take almost 2 years to complete when conducted sequentially, the FDA and CMS review processes for regulatory approval and reimbursement coverage can be substantial. In fiscal year 2013, CMS implemented six NCDs; the average time from analysis initiation to posting of the proposed NCD was 5.7 months, from proposed to final NCD an average of 86 days and an additional 132 days from final NCD posting to publishing of implementation instructions [19].

The FDA-CMS parallel review pathway
When conducted sequentially, the FDA and CMS review processes can take almost 2 years to complete [24]. To decrease the length of the review and approval process and to speed up patient access to important technologies, the FDA and CMS launched a ‘parallel review’ pilot program in October 2011 to partially align the review processes for regulatory approval and reimbursement coverage [25]. The parallel review process (Figure 2) establishes earlier CMS engagement and collaboration with the FDA and the manufacturer on pivotal clinical trial design and data review. This combined interaction encourages the early identification of potential trial design flaws and enables the manufacturer to adapt its protocol accordingly to satisfy the requirements of both the FDA and CMS. An added benefit of such an approach is the potential elimination of bottlenecks commonly associated with the traditional sequential review process without encroaching on the review standards of either agency. Ideally, a parallel review process reduces the interval between approval and securing coding coverage, as well as the time it takes to bring new products to patients.

The pilot program is scheduled to run until 13 December 2015, following an extension of the formerly proposed pilot phase, and is currently restricted to medical devices/diagnostics fulfilling one of the following criteria: new technologies for which the sponsor/requester has a pre-investigational device exemption (IDE) or an approved IDE application designation; new technologies that would require an original or supplemental application for PMA or a petition for de novo review or new technologies that fall within the scope of a Part A or Part B Medicare benefit category and are not subject to an NCD [25].

Further, the target population for the device may not fall within the Medicare benefit or may not meet the standard of ‘reasonable and necessary’ for diagnosis or treatment of an illness or injury.

Given that the majority of medical products approved by the FDA do not undergo NCD, it is envisioned that the parallel review pathway (if continued beyond the pilot phase) will still only accommodate a small number of innovations passing through the system, with priority designation for those technologies offering significant potential clinical benefits and requiring speedy dissemination to patients in need [26]. By shortening the gap between marketing approval and coverage decisions, products emerging out of a successful parallel review will reach patients more quickly. The pathway also offers a more harmonized and collaborative approach toward evidence generation that will ensure that the independent requirements of both agencies are met. To this end, manufacturers are encouraged to seek advice and input on clinical trial design from both the FDA and CMS at an early stage of a product’s development to ensure buy-in from all primary stakeholders [25].

Exact Sciences’ experience with the parallel review pathway
Cologuard became the first product to successfully navigate the FDA-CMS parallel review process on 11 August 2014, achieving simultaneous approval by the FDA and a preliminary NCD by CMS. The research necessary to develop Cologuard was significant. As required by the FDA, Cologuard had to demonstrate safety and efficacy in the intended target population and had to have sufficient non-clinical data to support laboratory analytical performance, quality controls and technical specifications of the device [18]. The FDA advised Exact Sciences on the study design and target patient population needed for the pivotal safety and efficacy clinical trial. CMS was involved in early conversations with Exact Sciences and confirmed that the Multi-Target Colorectal Cancer Screening Test for the Detection of Colorectal Advanced Adenomatous Polyps and Cancer trial, along with modeling data, was sufficient for establishing healthcare benefits in the Medicare population.
The pilot FDA-CMS parallel review pathway shortened the interval from FDA approval to CMS coverage for Cologuard. For Cologuard, 489 days elapsed between the PMA submission and the final CMS NCD. For comparison, the same review process for other NCDs implemented during fiscal year 2013 required an average of approximately 612 days (Figure 2) [21,24]. CMS representatives attended joint meetings with the FDA to learn about the product, review the supporting clinical data and understand the product label. This led to coverage and reimbursement early in the commercial launch of Cologuard, which was particularly important as Medicare covers a large portion of the target patient population for this product (Figure 3) [27].

The impact of NCDs extends beyond the 54 million beneficiaries covered under Medicare [27]. CMS’ policies undoubtedly influence the reimbursement decisions of other third-party payers, especially if the intended target population for an intervention is similar to the Medicare-eligible population [26]. Consequently, approving or denying coverage under Medicare can have an important impact on the commercialization and clinical adoption of medical products in the USA [26,28].

Healthcare insurers process over 5 billion claims for payment each year in the USA [29]. Importantly, a standardized coding system is needed to ensure that these payment claims are processed in an orderly and efficient manner. Medicare uses the Healthcare Common Procedure Coding System (HCPCS), a combination of two subsystems: level I and level II. Level I comprises Current Procedural Terminology (CPT) codes that are created and maintained by the America Medical Association. Level II comprises a standardized coding system, created and maintained by CMS, that is used primarily to identify products, supplies and services not identified by CPT codes. Several types of Healthcare Common Procedure Coding System level II codes exist; G-codes are used to identify professional healthcare procedures and services. Although the parallel review process does not address CPT coding and the establishment of a payment rate, a key contributing factor that allowed Exact Sciences to successfully launch Cologuard with Medicare beneficiaries was the issuance of a specific G-code that aligned with the positive NCD. The G-code (G0464) was issued in December 2014 with an effective date of 1 January 2015, thereby enabling Exact Sciences to secure Medicare reimbursement for Cologuard for the Medicare population [30]. The parallel review process shortened the time to issuance of a G-code. Exact Sciences was able to build on the issuance of a G-code and payment rate to secure a category 1 CPT code (and thus coverage) from commercial insurers, as not all of them recognize G-codes. Criteria for category 1 CPT codes are shown in Table 3 [31].

One challenge with the parallel review process was the need to coordinate a larger group of individuals, including not only stakeholders at the FDA, CMS and Exact Sciences, but also a wide array of consultants, biostatisticians and strategists at the same time rather than sequentially. This posed an
Table 3. Criteria for category I current procedural terminology code [31].

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All devices and drugs necessary for performance of the procedure or service have received FDA clearance or approval when such is required for performance of the procedure or service</td>
</tr>
<tr>
<td>2</td>
<td>The procedure or service is performed by many physicians or other qualified healthcare professionals across the USA</td>
</tr>
<tr>
<td>3</td>
<td>The procedure or service is performed with frequency consistent with the intended clinical use (i.e., a service for a common condition should have high volume, whereas a service commonly performed for a rare condition may have low volume)</td>
</tr>
<tr>
<td>4</td>
<td>The procedure or service is consistent with current medical practice</td>
</tr>
<tr>
<td>5</td>
<td>The clinical efficacy of the procedure or service is documented in literature that meets the requirements set forth in the current procedural terminology code change application</td>
</tr>
</tbody>
</table>

Expert commentary & five-year view
The FDA-CMS parallel review pilot, if continued, will have implications for the development and commercialization of future innovative diagnostics, as it provides an opportunity for communication with CMS early in the development process when decisions are made about study design and outcomes measurements. The evidence standard for FDA regulatory approval of new products is driven by statute and is fairly consistent whether or not one uses the parallel review process. However, the evidence standard to establish an intervention as reasonable and necessary for the Medicare population is less certain. The evidence requirements sought for Medicare coverage, in general, have become more stringent in recent years, with decisions pivoting on the provision of clinically meaningful data and very clear evidence of patient benefit [33]. Some believe that a positive NCD may be increasingly difficult to achieve. Chambers et al. recently evaluated all Medicare NCDs for medical interventions from February 1999 to August 2012, and found that the NCDs issued in the most recent quartile were approximately 20-times less likely to be positive than those issued in the first quartile, thus indicating that CMS has become increasingly restrictive in their coverage determinations [33]. As diagnostic technologies become more complex, CMS, and the commercial market in general, seem to be looking for more robust evidence to secure a diagnostic-related coverage and reimbursement.

If the need for more extensive outcomes data continues to grow, then alternative approaches to data generation may need to be considered. Premarket and post-market data collection can be used to mitigate the burden on IVD manufacturers, and the parallel review process is an effective mechanism to ensure that the needs of all parties are considered and captured in the evidence-generating strategies (e.g., clinical study designs, planned analyses).

It is also important to note that the FDA-CMS parallel review process does not include any linkage to coding and payment. Without this linkage, industry may be less likely to embrace a program that requires a significant investment to be successful. To address this gap, additional structure and policy changes may need to be implemented.

From the perspective of a device manufacturer, it is important that evidentiary standards for diagnostics in general remain consistent and are not increased as a result of a parallel review. The evidence standards for the parallel review process cannot become the floor as to how evidence is evaluated to bring a diagnostic test to market. An evidence bar that is too high, inconsistent or unclear creates a level of uncertainty for device manufacturers that poses an obstacle for commercialization and may stifle innovation. Conversely, device manufacturers need to consider how payers will view their products and recognize that FDA approval does not ensure coverage. Early consideration of payer evidence requirements will become increasingly important for medical devices seeking coverage reimbursement under Medicare. Exact Sciences benefited from its investment in a large-scale clinical trial that supported both the FDA approval and a CMS NCD that aided in securing coding, coverage and payment. Other diagnostic companies could similarly benefit from acknowledging the payer perspective when creating clinical testing programs and data collection plans as part of the device development process.

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Key issues

- Colorectal cancer is highly preventable if detected early, yet screening rates remain suboptimal, despite the availability of multiple screening methods.
- Cologuard® is a technologically advanced, non-invasive, multitarget stool DNA screening test for adults of either sex, 50 years or older, who are at typical average risk for colorectal cancer.
- The US FDA reviews the clinical safety and efficacy attributes of innovative class III in vitro diagnostics under a stringent premarket approval (PMA) process, which was a required intermediary step for Cologuard.
- Traditionally, Centers for Medicare & Medicaid Services (CMS) National Coverage Determinations involve a lengthy evaluation process to determine whether an FDA-approved product meets the reasonable and necessary threshold for national coverage under the Medicare benefit.
- In October 2011, the FDA and CMS launched a parallel review pilot program to partially coordinate the regulatory approval and coverage reimbursement procedures for selected products that meet specific criteria, with the aim of reducing delays in access to important new medical device technologies.
- The parallel review pathway offers a more harmonized and collaborative approach toward evidence generation, thereby ensuring that the independent requirements of both the FDA and CMS agencies are met.
- Cologuard became the first product to successfully navigate the FDA-CMS parallel review process. On 11 August 2014, Cologuard received simultaneous approval by the FDA and preliminary National Coverage Determination by CMS thus facilitating access for Medicare beneficiaries soon after launch.
- The parallel review process shortened the expected interval from FDA approval to CMS coverage for Cologuard.

References

Papers of special note have been highlighted as:

4. Important guidelines describing recommended screening practices for colorectal cancer.
8. Cologuard® label that provides additional details about the test and its intended use.


27. Excellent review and perspective on the FDA–Centers for Medicare & Medicaid Services parallel review pathway.


34. Analysis of National Coverage Determinations issued by Centers for Medicare & Medicaid Services (CMS) examining how CMS coverage policy has changed over time.