tests make them unavailable for the vast majority of patients in the world. Whether the tests are commercial or not, the use of large panels may identify unexpected mutations in some patients. These secondary findings may lead to social and psychological distress and all tested patients need to be informed of what may be the findings of a test using large panels and their consequences before being tested.

In most Western European countries, genetic counseling is well-organized and families with different members living in different countries can often be followed up adequately in their respective country. However, this is still not the case in other European and non-European countries, and we will have to, in the future, help these countries to organize their genetic cancer care programs, taking advantage of what has been already done successfully in others, for optimal and complete care of our GI cancer patients.

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When is off-label off-road?

Ideally, product labeling should include 'all clinical indications for which adequate data are available to establish the product's safety and effectiveness' [1]. For many reasons, this is not the case. Among generic medications, labeled indications often do not reflect the full range of indications for which there is compelling evidence of safety and effectiveness. For example, oxaliplatin, importantly used in gastric and pancreatic cancer is licensed by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) only for colorectal cancer. Omissions, such as these, weaken the mission of the licensing bodies for inclusiveness and have consequences for access to care in the many countries which limit coverage of medications to their licensed indications.

Even though the FDA and EMA licensed indications for recently developed expensive on-patent medications are more current and complete, their off-label use is increasing. This is largely due to increasing use of genomic testing and treatment recommendations based on tumor characteristics. This is motivated by the high unmet need for treatment options, exaggerated optimism regarding the patient's benefit from 'precision medicine' and the wish of patients and physicians to optimize outcomes. This trend coincides with increasing concerns about the off-label use of these agents, the costs of these drugs to patients and to the health care system and our ability to learn from off-label use.

The ESMO Guidelines do not often advice off-label use of this class of cancer drugs and if so, recommendations are indicated to be off-label. It is, however, easier to obtain reimbursement for off-label use in the USA than in Europe and ~30% of the therapies in the USA are estimated to be off-label use [2, 3].

The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 28 leading United States cancer centers that publishes regularly updated clinical practice guidelines. Last year, a critical report regarding the off-label use in the NCCN Guidelines as of 25 March 2016, concluded that the strength of the evidence supporting many of these off-label recommendations was weak [4]. Stimulated by this report the NCCN undertook a re-analysis of 44 off-label recommendations identified in the critical report [4] that is published in the current issue of this journal [5]. Of the 253 off-label uses across the 43 relatively novel expensive drugs reviewed they found that 91% were 'well-accepted off-label use', accompanied by either a category 1 (high-level evidence and NCCN consensus of appropriateness) or category 2A (lower-level evidence and NCCN consensus of appropriateness). Furthermore, a significant subset of these drugs was subsequently FDA approved or supported by randomized clinical trials (RCTs) [5]. Recommendations without RCT data, usually graded category 2A, were often for mechanism-based drugs with high response rates in rare cancers or subsets without effective therapies.

Given that there are deficiencies in the regulatory process and that there are substantial lacunae in the licensed indications, professional bodies and other organizations must fill the void in in providing high level evidence-based guidance. Guidelines such as those generated by NCCN and ESMO address this role.

Off-label guidance can be taxonomized relative to the regulatory process (Table 1). In some situations, off-label recommendations may be important to support. This applies to the therapies which are well supported by data and experience either in anticipation of approval (as was often the case in the study), expanding

Table 1. Off-label guidance taxonomized relative to the regulatory process

Off-label type regulatory process	Relationship to regulatory process	Justification for the treating physician	Example(s)
New approaches with compelling evidence of strong benefit that have NOT YET been approved (either in-process of regulatory review or will soon be submitted for regulatory review). These may include named patient and expanded access programs	Respectful, anticipatory	Patient beneficence: expert evaluation of data that there is major benefit and anticipation that it will pass review	Early uptake of maintenance olaparib in first remission for BRCA mutated ovarian cancer
Approaches approved by regulatory authority BUT not for this specific subgroup of patients	Justifiable extrapolation	Patient beneficence: evaluation that the target population in the label is excessively narrow and that there is justifiable reason to anticipate benefit in a wider patient group	CDK 4/6 inhibitors for premenopausal women with ovarian suppression Guidance on prescribing for children, pregnant women, patients with organ failure, patients with poor performance status Use of durvalumab for stage III NSCLC PD-L1 expression <1% (based on ITT data)
Approaches, supported by adequate data, that have not been submitted for regulatory review and are not likely to be submitted (for example rare diseases, generic medicine with no sponsor, evidence not compliant with regulatory requirements)	Substitute expert review	Deficiencies and stringencies in the regulatory process (such as very high sponsor cost and regulatory inflexibilities) discourage submission for rare diseases, off-patent medications and indication expansion	FLOT/FOLFIRINOX chemotherapy (oxaliplatin off-patent) Immunotherapy for MSI-H/dMMR tumors (in Europe)
Approaches that have been submitted for regulatory review and which were rejected	Undermining	Disregard of a negative regulatory authority evaluation	NCCN recommendation of bevacizumab with chemotherapy in patients with recurrent or stage IV HER2 negative breast cancer
Approaches with weak evidence of benefit that have not been submitted for regulatory review and are not likely to be submitted	Undermining	Consideration of any therapeutic option that may be of patient benefit. Precision medicine with low ESCAT grade	Immune checkpoint inhibitors in settings where level of benefit is so low that the manufacturer has not submitted application for indication approval

T-DM1, trastuzumab emtansine; CDK 4/6, cyclin-dependent kinase 4/6; NSCLC, non-small-cell lung cancer; ITT, intention to treat; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, oxaliplatin; MSI-H, microsatellite-instability-high; dMMR, mismatch repair-deficient; NCCN, National Comprehensive Cancer Network.

the scope of application or supplementing the approval registration process when there has been none. These must be distinguished from off-label endorsements that undermine the regulatory process either by contradicting explicit regulatory findings or by endorsing approaches with very weak evidence for benefit (Table 1). Recommendations such as these are harmful: they undermine the authority of the regulatory process and may have adverse effects on the cost of care, prudent resource allocation and even patient readiness to participate in research.

Although NCCN has described how expert panels develop their guidelines and gradings [6], recommendation categories are not always listed, and it is still difficult to determine the recommendation category without being part of the expert committee. This issue is important given that NCCN guidelines are consulted worldwide.

There are now several initiatives to support future rational and responsible off-label use, particularly in the setting of 'precision medicine' practices.

ESMO developed the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) in which grades the evidence-base for therapeutic interventions based on identified 'actionable' genomic alterations [7]. Approaches with a high ESCAT grade, well supported by data, will usually also have a ESMO-Magnitude of Clinical Benefit Scale grade further indicating well established benefit [8, 9].

Another option to get more insight into relevance of registered drugs for off-label indications is to perform clinical trials with precision medicine driven off-label use of drugs and translate findings to a 'learning health care system'. It is argued that drug pricing is related to the cost of development including large scale clinical testing. Randomized phase III studies are expensive, and pharma mostly focuses its efforts on areas where there is a relatively high volume of patients. It is also clear that the new drugs have potential in areas where the incidence of the drug target is less prevalent. This means, in theory, that off-label use of drugs could be used to identify indications that benefit from these

drugs. However, our current health care system does not facilitate a 'learning health care system'. In general, there are no structured clinical data collections of the outcome of off-label use. In the Netherlands, this approach has been incorporated into a 'Drug Rediscovery Protocol' (acronym DRUP) study (ClinicalTrials.gov Identifier: NCT02925234). DRUP serves as a platform where patients can be treated with off-label targeted agents whilst collecting all relevant outcome data. This approach improves access to these off-label drugs, diminishing inequalities in care, ensures robust review of target and treatment selection, and prospectively collects outcome data to be shared with industry, payers and regulatory bodies. This study, initiated in 2016, now has over 26 approved targeted drugs at its disposal. Data from this study led to a pay-for-performance system [10] for nivolumab in patients with MSI-high tumors (no approved drug available in Europe for this indication) whereby the manufacturer provides nivolumab for free during the first 16 weeks of treatment with payer commitment to reimbursement for responding patients. Negative findings are shared with the scientific community in order to prevent repetitive treatments without the outlook of clinical benefit. Several countries are now using similar protocols [e.g. TAPUR (NCT02693535) and CAPTUR (NCT03297606)] which specifically allow data sharing.

In conclusion, while we are grateful for all the novel drugs that have been developed for cancer, we have an obligation to maximize the clinical value for our patients and communities. These dual obligations require commitments to rational off-label use and to structured learning through data collection and sharing in order to identify those approaches that deserve to become licensed indications and to be reimbursed. Importantly, this allows us to distinguish them from those that are inadequately effective to justify licensing or clinical recommendation.

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Is the tumour microenvironment a critical prognostic factor in early-stage colorectal cancer?

The TNM staging system remains the cornerstone of risk assessment in patients with early-stage colorectal cancer (CRC). However, clinical behaviour is diverse within the same stages, making prognostication an imprecise science. Microsatellite instability (MSI) is the only biomarker routinely considered beyond TNM, although a range of major genomic changes is well established, with contradictory evidence in outcome prediction [1, 2]. So what other markers could improve prognostic precision?

CRC heterogeneity has now been comprehensively characterised at the transcriptomic level as between three and six prognostic and potentially predictive subtypes [3–8]. For clinical application, these competing subtypes were integrated into four consensus molecular subtypes (CMS1–4) by the ColoRectal