From:	Stark, Paul
To:	Eligibility2019; 112Guidance2019
Cc:	Susalka, Stephen; Lori Pressman
Subject:	AUTM Comments on §§101, 112 Guidance
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Dear Under Secretary Iancu:
Thank you for the opportunity to comment on the §101 subject matter eligibility guidance and the §112 guidance on examining computer–implemented functional claim limitations posted in the Federal Register January 7, 2019.
Attached are AUTM's comments.
Paul

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March 8, 2019

The Honorable Adrei iancu
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
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Via email: *Eligibility2019@uspto.gov*
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AUTM Comments on §101 Subject Matter Eligibility Guidance and §112 Guidance on Examining Computer–implemented Functional Claim Limitations

Dear Under Secretary Iancu:

Thank you for the opportunity to provide comments on the §101 subject matter eligibility guidance and the §112 guidance on examining computer–implemented functional claim limitations posted in the Federal Register January 7, 2019.

The U.S. Chamber of Commerce's 2019 IP Index shows that IP protections increase countries' global competitiveness and "strong IP systems are the driving force behind the innovations that … enrich life, address global problems, and achieve unpredictable progress."[i] Having an effective IP system also drives investments and allows concentration of resources and research and development.

AUTM is very supportive of Director Iancu's leadership at the USPTO and his commitment to providing a strong, reliable, and predictable intellectual property system. Until there is new legislation, Director Iancu's guidances will benefit our national innovation ecosystem, and together are a useful step toward creating a clearer and more predictable scope of enforceable patent protection.

AUTM's response to the NIST RFI contained the following paragraph:

Proposed Solution 1B: Issue a USPTO guidance on the use of the first step of the Mayo - Alice test: "Determine if the claim at hand is directed to a law of nature, a natural phenomenon, or

an abstract idea," requiring the examiner to support that finding with evidence. The examiner should be required to identify the natural law, natural phenomenon, or abstract idea, and show that it is highly predictive and not merely sometimes observed in association with a particular outcome. This clarification would restore a class of meritorious insights into use of naturally occurring molecules with otherwise unpredictable effects unless used, prepared, purified, or administered according to the claimed invention. It would restore the breadth of §101, and rely on the existing enablement and written description requirements, as well as the existing novelty and non-obviousness standards.

Thus, we look favorably on the "2019 Revised Patent Subject Matter Eligibility Guidance" concerning the judicial exceptions, which instructs examiners to "Evaluate whether the judicial exception is integrated into a practical application", and if it is, to deem it patent eligible.

We also look favorably on the guidance on "Examining computer-implemented functional claim limitations for compliance with 35 U.S.C. §112", as description sufficient to enable one of ordinary skill in the art to practice the claimed invention is at the heart of the patent system. As noted in the guidance, a description sufficient to enable the scope of the claimed invention also serves to demonstrate that the applicant was in possession of the invention at the time of filing.

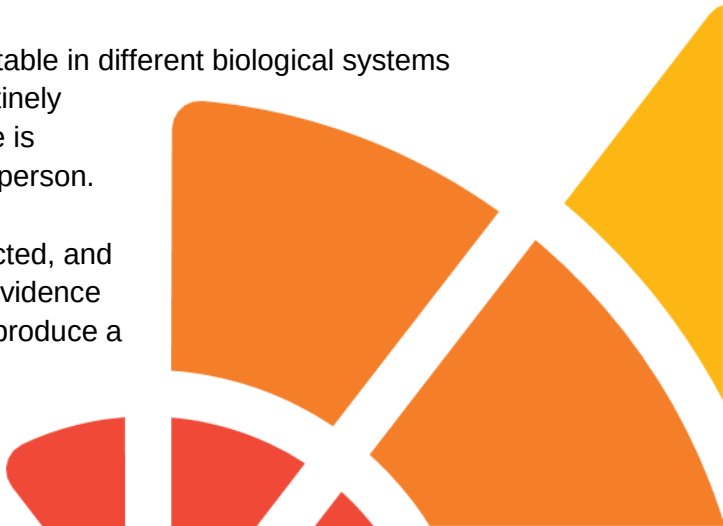
The combination of broad scope of patent eligible subject matter together with prudent adherence to and implementation of other statutory requirements, such as §§ 102, 103, and 112 are welcome.

As described in the Bilskiblog: Bad Science Makes Bad Patent Law—No Science Makes It Worse, parts I[ii] and II[iii], natural laws and phenomena are characterized as such because they make predictions which have not yet been falsified (natural laws) or are widely observed to exist absent human intervention (natural phenomena).

Scientific criteria, not legal criteria, are needed to characterize laws of nature or natural phenomena as such. Certain patents about correlations have been invalidated under §101 being as embodiments of natural laws. Certain patents about molecules have been invalidated under §101 as being "products of nature", and as such natural phenomena.

Predictions about naturally occurring biological systems are notoriously imprecise. The Patent Office recognizes that some arts are more predictable than others in its enablement guidance[iv]. Biology is acknowledged not to be a "predictive" art.

Molecules, such as new drug formulations, are unpredictable in different biological systems because they behave differently. For example, they routinely behave differently *in silico*, *in vitro*, and *in vivo*, and there is significant variability and unpredictability from person to person. There are hundreds of thousands of clinical trials, the overwhelming majority of which do not proceed as expected, and which were undertaken with a great deal of pre-clinical evidence gathered to select only those molecules mostly likely to produce a desirable, and predicted effect.



Additionally, as we move toward more personalized treatments and therapies, there is evidence that markers, such as molecules or groups of molecules[v], [vi] which help recruit and retain patients for clinical trials increase the likelihood of approval of the treatment. There are also markers which can identify patients who are not likely to benefit from treatments, or who are likely to have an adverse side effect. There are also markers to identify patients who are likely to benefit from more frequent monitoring.

Evidence exists that there is a large challenge of finding and validating predictive markers; even as challenging as finding a treatment which is effective[vii]. This evidence suggests that using markers to identify patients likely to benefit from certain treatments, or more broadly, to manage care, (such as by avoiding certain treatments or more frequent monitoring) is a practical application, and therefore that disclosing the use of such markers and the evidence supporting such use is deservedly patent eligible under §101.

These remarks on markers are not limited to types of molecules, or to molecules themselves. There are also markers which are derived from images or they may be a physiochemical marker (a marker based on the physical chemical properties of molecules)[viii]. Sometimes molecules are initially characterized by their function, and are given names which appear to turn them into abstract ideas, but then, in actuality, a later understanding of such molecules changes to clarify that the molecules themselves are not abstract ideas[ix].

Scientific understanding and technology are evolving rapidly in the twenty first century. A 2016 Master's Thesis in Innovation Sciences from Utrecht University[x] reports patents on diagnostic products foster product development.[xi] Therefore, there is a pressing need for a strong, stable, and predictable patent system with patentability criteria applied thoughtfully and consistently. These timely guidances foster such stability and predictability, and as such provide strength in an IP system and foster the Constitutional mandate of promoting the progress of science and useful arts.

Sincerely,

Stephen J. Susalka

Stephen J. Susalka, PhD, RTTP, CLP
AUTM CEO

[i] https://www.uschamber.com/series/above-the-fold/2019-ip-index-shows-ip-protections-increase-countries-global-competitiveness

[ii] http://www.bilskiblog.com/blog/2016/09/bad-science-makes-bad-patent-law.html

[iii] http://www.bilskiblog.com/blog/2016/09/bad-science-makes-bad-patent-law-no-science-makes-it-worse-part-ii.html

[iv] 2164.03 Relationship of Predictability of the Art and the Enablement Requirement [R-08.2012] https://www.uspto.gov/web/offices/pac/mpep/s2164.html

[v] Thomas, David W., Burns, Justin, Audette, John , Carol, Adam, Dow-Hygelund, Corey, Hay, Michael. 2016. "Clinical Development Success Rates 2006-2015", Prepared by BIO, Biomedtracker and Amplion, 2016 https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

> Page 18, figure 9. "Patient Selection Biomarker Programs: The use of biomarkers as inclusion or exclusion criteria, or 'selection biomarkers', for enrolling patients into clinical studies has increased dramatically since the sequencing of the human genome. ….The LOA [likelihood of approval] from Phase I can be found in Figure 9. The benefit from selection biomarker use raises the LOA from Phase I to one in four [25.9%] compared to less than one in 10 [8.4%]when no selection biomarker was used."

[vi] Wong, Chi Heem, Siah, Kien Wei, Lo, Andrew W. 2018."Estimation of clinical trial success rates and related parameters, *Biostatistics",* (January 31) 00, 00 1–14 https://academic.oup.com/biostatistics/advance-article/doi/10.1093/biostatistics/kxx069/4817524

> Page 8: "Trials using biomarkers exhibit almost twice the overall POS (POS1,APP) compared to trials without biomarkers (10.3% vs. 5.5%). While the use of biomarkers in the stratification of patients improves the POS in all phases, it is most significant in Phases 1 and 2. (We caution against over-interpreting the results for therapeutic areas outside oncology due to their small sample size.) These findings are similar in spirit to the analysis by Thomas *and others* (2016), which also found substantial improvement in the overall POS when biomarkers were used"

[vii] Id.

> Page 8: "However, when we expanded the definition of a biomarker trial to include trials with the objective of evaluating or identifying the use of any novel biomarker as an indicator of therapeutic efficacy or toxicity, in addition to the selection of patients, we obtained significantly different results (see Table S3 in Section A6 of the supplementary material available at *Biostatistics* online). Instead of finding a huge increase in the overall POS, we find no significant difference. It may be that trials that attempt to evaluate the effectiveness of biomarkers are more likely to fail, leading to a lower overall POS compared to trials that only use biomarkers in patient stratification"

[viii] Sina, Abu Ali Ibn, Carrascosa, Laura G., Lian, Ziyu, Grewal, Yadveer S., Wardiana, Andri, Shiddiky, Muhammad H.A., Gardiner, Robert A., Samaratunga, Hemamali, Gandhi, Maher K., Scott, Rodney J., Korbie, Darren, Trau, Matt. 2018 "Epigenetically reprogrammed methylation landscape drives the DNA self-assembly and serves as a universal cancer biomarker", Nature Communications Dec 4; 9(1):4915. https://www.ncbi.nlm.nih.gov/pubmed/?term=methylscape

> Abstract: "Epigenetic reprogramming in cancer genomes creates a distinct methylation landscape encompassing clustered methylation at regulatory regions separated by large intergenic tracks of hypomethylated regions. This methylation landscape that we referred to as Methylscape is displayed by most cancer types, thus may serve as a universal cancer biomarker. To-date most research has focused on the biological consequences of DNA Methylscape changes whereas its impact on DNA physicochemical properties remains unexplored. Herein, we examine the effect of levels and genomic distribution of methylcytosines on the physicochemical properties of DNA to detect the Methylscape biomarker. *We find that DNA polymeric behaviour is strongly affected by differential patterning of methylcytosine, leading to fundamental differences in DNA solvation and DNA-gold affinity between cancerous and normal genomes.* [emphasis added] We exploit

these Methylscape differences to develop simple, highly sensitive and selective electrochemical or colorimetric one-step assays for the detection of cancer. These assays are quick, i.e., analysis time ≤10 minutes, and require minimal sample preparation and small DNA input."

[ix] Gerstein, Mark B., Bruce, Can, Rozowsky, Joel S., Zheng, Deyou, Du, Jiang, Korbel, Jan O., Emanuelsson, Olof, Zhang, Zhengdong D., Weissman, Sherman, Synder, Michael 2007 "What is a Gene, Post-Encode? :History and Updated Definition". Genome Res. 2007. 17: 669-681 https://www.ncbi.nlm.nih.gov/pubmed/17567988

Abstract: "While sequencing of the human genome surprised us with how many protein-coding genes there are, it did not fundamentally change our perspective on what a gene is. In contrast, the complex patterns of dispersed regulation and pervasive transcription uncovered by the ENCODE project, together with non-genic conservation and the abundance of noncoding RNA genes, have challenged the notion of the gene. To illustrate this, we review the evolution of operational definitions of a gene over the past century—from the abstract elements of heredity of Mendel and Morgan to the present-day ORFs enumerated in the sequence databanks. We then summarize the current ENCODE findings and provide a computational metaphor for the complexity. *Finally, we propose a tentative update to the definition of a gene: A gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products.* [Emphasis added] Our definition side-steps the complexities of regulation and transcription by removing the former altogether from the definition and arguing that final, functional gene products (rather than intermediate transcripts) should be used to group together entities associated with a single gene. It also manifests how integral the concept of biological function is in defining genes."

[x] Gottardi, Simone, August 2016 "The effects of patenting on development of diagnostics products". Master Thesis Innovation sciences, Utrech University". https://dspace.library.uu.nl/handle/1874/339078

Summary
In 1998 Heller and Eisenberg raised concerns that patenting of genes could be counter to the common social interest. This sparked extensive research on the effect of gene patenting on research and product development. To date there is a lack of a comprehensive picture of the effects of gene patenting on product development. We operationalize this research gap by analyzing how patents influence market niche based on gene patenting and those based on other biological patents. To test the effects we sampled 288 market niches for diagnostic products approved by the FDA and we linked them to 1199 patents in the USPTO and 1602 licensing agreements. We test whether different qualities of patenting affects the rate of incremental innovation, the strength of monopoly and the strength of the barriers to entry in a market niche. The results show that patenting of genes does not have different effects than other type of patenting, thus the concerns of raised by Heller and Eisenberg on product development remain unsubstantiated.

[xi] Id. Page 47

How does gene patenting influences the quality of diagnostic products supply?

The results indicate that gene patenting does not affect the quality of diagnostic products in any particular way. However, they do have an effect on product development as any other patent.

Moreover, the results showed that the effects of patenting in product development have opposite effects than what is seen in research, while scientists are attracted to research in field where there is no patents, companies are drawn to develop products in fields where patents are present.