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Regeneron Genetics Center and Geisinger Study Finds Life-Threatening Genetic Disorder is Substantially Underdiagnosed

TARRYTOWN, N.Y., Dec. 22, 2016 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Geisinger Health System (Geisinger) today announced that *Science* has published their study finding that a life-threatening genetic disorder known as Familial Hypercholesterolemia (FH) is both underdiagnosed and undertreated. It was published alongside a foundational paper providing the first overall description of the Geisinger-Regeneron Genetics Center (RGC) collaboration known as DiscovEHR.

The Geisinger-RGC collaboration examined genetic variants causing FH in the first 50,726 Geisinger patients participating in the MyCode Community Health Initiative. It then compared the findings against the de-identified medical histories of these patients as contained in Geisinger electronic health records.

"Being able to connect patients' de-identified medical records with their DNA data is an advantage that few others in this field have, particularly with this large number of patients. Paired with the RGC's unique technological and analytical resources, we are able to make meaningful discoveries that may advance the implementation of precision medicine today and the development of new or improved medicines tomorrow," said Noura Abul-Husn, M.D., Ph.D., Associate Director of Translational Genetics at the RGC and co-author of the paper.

Traditionally, in the United States, FH is diagnosed in patients with high cholesterol who also have a family history of early heart attacks and strokes. Genetic testing for FH is currently uncommon in clinical practice. Results of the new study found many undiagnosed cases of FH and helped to define the extent of FH in the general population and the extent to which it is systemically undertreated.

"The study shows us that FH is about twice as common as it was once thought to be, and that large-scale genetic testing for FH helps identify cases that would otherwise be missed," said Michael F. Murray, M.D., Director of Clinical Genomics at Geisinger. "We now hope to use DNA sequencing to guide better management for patients."

"FH is a serious disease that can have severe consequences for some people, but also has available treatment options," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer, Regeneron. "We hope that this study will drive higher awareness of the prevalence of FH, since with greater vigilance more patients could be accurately diagnosed and treated with effective therapies."

FH is caused by a defect that makes the body unable to remove "bad" cholesterol from the blood. This cholesterol (low density lipoprotein cholesterol or LDL-C) then accumulates, often undetected, and can lead to early death from heart attacks or stroke - even in very young people.

One of the study's many findings was that 1 in every 256 people has a disease-causing mutation, or variant, in one of the three FH genes. It showed that participants with a deleterious FH gene variant had significantly higher "bad" cholesterol than those without an FH gene variant. They also had significantly increased odds of both general and premature coronary artery disease.

The study identified 35 mutations, or variants, in the genes that have been previously determined to cause FH: *LDLR*, *APOB* and *PCSK9*. Only 24 percent of people who carry FH-causing variants had sufficient criteria within their electronic health records to support a probable or definite FH diagnosis, meaning that without genetic confirmation, many of these patients would go undiagnosed and potentially be undertreated. Consistent with this, 42 percent of people with these FH-causing variants did not have a recent active prescription for statins, the first line therapy for cholesterol lowering. Among statin-treated people with FH-causing variants, less than half met goals for cholesterol lowering, suggesting the need for additional cholesterol-lowering therapy.

Interestingly, FH variants explained only 2.5 percent of severe hypercholesterolemia (defined as LDL-C levels over 190 mg/dl) in the cohort, which challenges the notion that patients with very high LDL-C levels are likely to have genotypically defined FH and likely represents yet another large group of individuals that are initially undertreated.

"Geisinger is committed to translating this important research directly into improved care for our patients," said David H. Ledbetter, Ph.D., Executive Vice President and Chief Scientific Officer at Geisinger. "We have begun a major effort to confirm individual patient findings and inform individual participants and their doctors when genetic findings, that are known

to cause illness, are discovered in our population," he said.

FH is one of 27 genetic conditions being targeted at Geisinger. So far, nearly 200 patients have already been informed they carry one or more disease-causing genetic mutations with consequences that can be treated. These conditions are mainly related to risk for cancer or cardiovascular illness. The effort to return individual results will continue as more findings are confirmed. For details see go.geisinger.org/results.

About MyCode

The MyCode Community Health Initiative is a precision medicine project, originally launched in 2006, at Geisinger Health System in which Geisinger patient-participants have consented to donate blood and other biological samples to a system-wide biobank designed to store those samples for wide research uses and for genomic or precision medicine.

About DiscovEHR

The DiscovEHR human genetics study population for this analysis includes 50,726 adult Geisinger Health System patients who consented to participate in the MyCode Community Health Initiative. More than 125,000 MyCode participants have consented into the program to date. MyCode volunteers have given informed consent to allow sharing of de-identified electronic health records, provide samples that can be linked to their health records for broad research, and permit re-contact for additional studies. Electronic health records for the group in this DiscovEHR study are available for a median of 14 years of clinical care.

For MyCode participants who are suspected to harbor a pathogenic variant in one of the 76 clinically actionable genes, Geisinger will confirm preliminary research findings in a lab facility that is certified to the Clinical Laboratory Improvement Amendments (CLIA) Act, the federal standard for clinical testing. Qualified Geisinger personnel will provide the results of confirmatory CLIA-certified testing to patients and their primary care providers along with genetic counseling and appropriate referrals to other specialists.

About Geisinger

Geisinger Health System is an integrated health services organization widely recognized for its innovative use of the electronic health record and the development of innovative care delivery models such as ProvenHealth Navigator® and ProvenCare®. As one of the nation's largest health service organizations, Geisinger serves more than 3 million residents throughout 45 counties in central, south-central and northeast Pennsylvania, and also in southern New Jersey with the addition of AtlantiCare, a National Malcolm Baldrige Award recipient. The physician-led system is comprised of approximately 30,000 employees, including nearly 1,600 employed physicians, 12 hospital campuses, two research centers and a 551,000-member health plan, all of which leverage an estimated \$10.5 billion positive impact on the Pennsylvania and New Jersey economy. Geisinger has repeatedly garnered national accolades for integration, quality and service. In addition to fulfilling its patient care mission, Geisinger has a long-standing commitment to medical education, research and community service. For more information, visit www.geisinger.org, or follow the latest Geisinger news and more on [Twitter](#) and [Facebook](#).

About the Regeneron Genetics Center

The RGC is a fully integrated genomics program that spans early gene discovery and functional genomics and facilitates drug development. The primary goal of the RGC is to improve patient outcomes by identifying novel drug targets, clinical indications for development programs, and genomic biomarkers for pharmacogenomic applications. The RGC is tackling various sequencing (exomes, targeted sequencing, etc.) and analytical approaches and has established numerous collaborations with leading human genetics researchers. To enable this large-scale sequencing and analysis program, the RGC utilizes fully-automated sample preparation and data processing, as well as cutting-edge cloud-based informatics. Including efforts with Geisinger, the RGC has sequenced de-identified DNA from more than 130,000 individuals to date and is now sequencing at a rate of 150,000 individuals per year.

About Regeneron Pharmaceuticals, Inc.

Regeneron (NASDAQ: REGN) is a leading science-based biopharmaceutical company that discovers, invents, develops, manufactures and commercializes medicines for the treatment of serious medical conditions. Regeneron commercializes medicines for eye diseases, high LDL cholesterol and a rare inflammatory condition and has product candidates in development in other areas of high unmet medical need, including rheumatoid arthritis, atopic dermatitis, asthma, pain, cancer and infectious diseases. For additional information about the company, please visit www.regeneron.com or follow @Regeneron on Twitter.

Regeneron Forward-Looking Statements and Use of Digital Media

This press release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications

of Regeneron's products, product candidates, and research and clinical programs now underway or planned, including without limitation the use of human genetics in Regeneron's research process; the extent to which the results from Regeneron's research programs (such as the DiscovEHR collaboration between the Regeneron Genetics Center and Geisinger Health System discussed in this news release) or preclinical testing may lead to advancement of product candidates to clinical trials or therapeutic applications; unforeseen safety issues resulting from the administration of products and product candidates in patients, including serious complications or side effects in connection with the use of Regeneron's product candidates in clinical trials; the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates and new indications for marketed products; ongoing regulatory obligations and oversight impacting Regeneron's marketed products, research and clinical programs, and business, including those relating to patient privacy; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's products and product candidates; competing drugs and product candidates that may be superior to Regeneron's products and product candidates; uncertainty of market acceptance and commercial success of Regeneron's products and product candidates; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; coverage and reimbursement determinations by third-party payers, including Medicare and Medicaid; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its sales or other financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi and Bayer HealthCare LLC (or their respective affiliated companies, as applicable), to be cancelled or terminated without any further product success; and risks associated with third party intellectual property and pending or future litigation relating thereto. A more complete description of these and other material risks can be found in Regeneron's filings with the U.S. Securities and Exchange Commission, including its Form 10-K for the fiscal year ended December 31, 2015 and its Form 10-Q for the quarterly period ended September 30, 2016. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update publicly any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.

Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (<http://newsroom.regeneron.com>) and its Twitter feed (<http://twitter.com/regeneron>).

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