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Directed Evolution Is the Environmental Solution

Within the last decade, the growing concern to save our environment has encouraged companies across the globe to be more conscientious about the quality of their products by offering greener alternatives to every day solutions. As mindful consumers, we share in this responsibility by adopting healthier and greener lifestyles to produce less waste, recycle biodegradable materials and use environmentally-safe chemicals.

Dr. Merkin’s unique perspective as Innovation, Technology, Legislation and Care Delivery come together to impact the future of population health.
Critical discussions have also forced the most powerful leaders of our time to focus their attention on protecting our natural resources and finding solutions to successfully manage our planet’s ecosystems. The destructive effects of pollution and other man-made disruptions can potentially threaten entire ecosystems that affect not only our health but our entire way of life.

In our feature article, Frances H. Arnold, Linus Pauling Professor of Chemical Engineering, Bioengineering and Biochemistry along with her lab at the California Institute of Technology in Pasadena, CA (Caltech) pioneered a way to impact the world through the directed evolution of enzymes. Arnold has developed bacteria that produce high-energy carbon rings made up of carbon-silicon and carbon-boron bonds, neither of which is found among organisms in the natural world. Suddenly, the world has been given high-speed access to cleaner, safer and greener alternatives previously not available.

From biofuels to pharmaceuticals, Arnold’s discoveries provide companies and businesses throughout the world the ability to create safer, more effective solutions to replace dangerous chemicals and materials currently utilized today. Through her relentless pursuit of creating and supporting a greener society, she has earned the well-deserved recognition of being the fifth woman in history to be awarded the 2018 Nobel Prize in Chemistry.

We will continue to support the efforts and research of the brilliant scientists and professors at Caltech as we look forward to witnessing some of the most important discoveries of our lifetime.

Richard Merkin, M.D.
President and CEO of HPN

Richard Merkin, M.D.
Healthcare visionary Dr. Richard Merkin has spent the last 40 years implementing a successful, workable business model to address the needs and challenges of affordable managed healthcare.
A NOBEL PRIZE FOR THE AGES
As a Nobel Laureate, she has altered the natural progression of evolution in such a way that would further inspire her peers and colleagues in the scientific community. “If you’re going to change the world, you’ve got to try really different things,” Arnold shared during an interview with Ph.D. student Sofie Ährlund-Richter from the Department of Neuroscience at Karolinska Institute in Stockholm, Sweden. Simply put, Arnold not only figured out a way to expedite evolution, but by doing so has opened up a world of possibilities to significantly transform the world around us.

**DIRECTED EVOLUTION OF ENZYMES**

To grasp the depth of Arnold’s research using enzymes requires understanding how directed evolution is able to create
new molecules to solve human problems. By using chemistry, molecules are altered and bred for very specific functions. Directed evolution manipulates enzymes to react in ways enzymes had not catalyzed before. While many scientists commonly use rare metals such as platinum to create a reaction, Arnold found a way to replace these toxic metals, thus resulting in producing safer and more sustainable products and materials. Enzymes also now have the ability to make substances with bonds that do not occur in biology, such as bonds between carbon and silicon and carbon and boron. These newly-created enzymes have the potential to impact humanity in

### Nobel Prize Trivia

- Frances H. Arnold is 1 of 5 women to ever win a Nobel Prize in Chemistry.
- She is 1 of 17 women to win in a science-based category (Physiology, Medicine, Chemistry or Physics).
- Between 1901 and 2018 the Nobel Prize and Prize in Economic Sciences have been awarded 52 times to women.¹

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¹ Source: www.nobelprize.org/prizes/facts/nobel-prize-facts

Image courtesy of Caltech
revolutionary ways, from their ability to remove stains from clothing and other materials to becoming instrumental in targeting and curing disease. One example of directed evolution’s profound effect in the field of medicine was in 2010 when Merck, one of the largest pharmaceutical companies in the world, in partnership with Codexis, developed an enzymatic process for producing the active ingredient in Januvia™, a drug used in the treatment of type 2 diabetes.

“If you’re going to change the world, you’ve got to try really different things.”
~ Frances Arnold

PAYING IT FORWARD
The prestigious recognition of winning the Nobel Prize comes with a financial reward that can provide recipients the boost and support they need to help fund their next revolutionary discovery. When asked about her plans to use the award, or if there are any charities she would contribute toward, Arnold proudly mentioned donating the money to charity, and specifically sharing some of the funds with the California Institute of Technology (Caltech) where she is currently a professor.

She was quoted as saying, “Caltech would be an excellent place to put some of it. It’s a jewel of a place. Everyone is brilliant. People talk to each other. We get the smartest students in the world and we have this attitude that you should think big and solve really important problems.”

“Frances is one of the most singularly inspiring researchers I know. She challenged convention in the way she approached the engineering of proteins, and revolutionized this whole field,” adds Professor Mikhail Shapiro, Arnold's fellow colleague and Professor of Chemical Engineering and Heritage Principal Investigator at Caltech.

“I have known Frances since I was a Ph.D. student at MIT and collaborated with her. My main reason for wanting to join Caltech as a faculty member was to have colleagues like Frances who would inspire me and my group to pursue big, transformative ideas. Now, my office is just across the hall from hers, and her lab is just upstairs from mine. Besides being an inspiring scientist, Frances has been a strong

What is directed evolution?
The manmade procedure, known as directed evolution of enzymes and binding proteins, is built on molecular insights which move the process of evolution from the natural world into the laboratory and further speed up the development. The procedure relies on intended variation of protein sequences at a defined level of randomness.
Directed Evolution of Enzymes

1. Random mutations are introduced in the gene for the enzyme that will be changed.

2. The genes are inserted in bacteria, which use them as templates and produce randomly mutated enzymes.

3. The changed enzymes are tested. Those that are most efficient at catalysing the desired chemical reaction are selected.

4. New random mutations are introduced in the genes for the selected enzymes. The cycle begins again.

After a few cycles of directed evolution, an enzyme may be several thousand times more effective.
force in bringing together people in the Caltech community who are interested in the interface between engineering and biology.”

Arnold’s directed evolution of enzymes also resulted in winning the 2019 Bower Award for Achievement in Science. The Bower Award is among the prestigious Franklin Institute Awards which honors exceptional innovators in science and technology.

**CALTECH: THE COMMON GROUND FOR SUCCESS**

Frances Arnold along with Merkin Fellows and Heritage Investigators, past and present, who have chosen to expand their knowledge and coach the next generation of brilliant minds at Caltech share common traits, characteristics and values that exemplify excellence. They not only embrace and support an open community for knowledge-sharing, but share a profound commitment, mindset and discipline, determination and passion to create solutions from the simplest of problems to the most complicated issues that face humankind. By using methods and techniques that challenge the natural course of science, medicine, and evolution, the scientists at Caltech bring what seemed nearly impossible just years ago into life-changing reality.

“I believe some of the greatest breakthroughs will occur in this century, and I think Caltech is particularly positioned to be a leader in delivering solutions in many fields of study,” adds Dr. Richard Merkin, President and CEO of Heritage Provider Network. “HMRI is proud to support Caltech’s continued efforts to innovate science and technology to create a lasting impact on the world.”

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**ARNOLD’S KEY ACCOMPLISHMENTS**

2005: Co-founded the Gevo company, whose mission is “to replace fossil-based fuels and chemicals with low carbon, cleaner options while generating products that help feed the world.” Arnold’s work has helped Gevo utilize yeast to produce isobutanol which is used in place of ethanol in making fuel.

https://www.chevron.com/

2013: Co-founded the company Provivi that produces natural, safe and effective pest control. As a Caltech trustee, Dr. Richard Merkin had the opportunity to discuss with Dr. Arnold how the science behind Provivi can have a positive impact on healthcare. Provivi is aligned with the types of goals and objectives we have at HPN, and Heritage provided support to help launch the company. The company uses Dr. Arnold’s techniques to alter insect pheromones so that crop pests are unable to reproduce. Provivi’s methods provide a cost-effective alternative to pesticides and help reduce the use of chemicals harmful to people and the environment.

https://www.provivi.com

2018: Awarded the Nobel Prize in Chemistry for her work on directed evolution of enzymes and binding proteins, which includes the development of esterases for the pharmaceutical industry, thermophilic enzymes, enantioselective syntheses for pharmaceutical, insecticidal and herbicidal products, and enabled biocatalytic synthesis of novel natural products, such as carotenoids³.

³ Source: www.news.berkeley.edu/2018/10/03/chemistry-nobel-goes-to-uc-berkeley-ph-d-frances-arnold
American Heart Association’s (AHA) annual Heart Walk in support of the organization’s efforts to raise funds and awareness for heart disease, the number one cause of death in the U.S. for both men and women. DOHC continued to carry forward the “Life is Why” message for good heart health as it geared up for the AHA’s annual Go Red for Women event held in February, American Heart Month, to help spread the news that nearly 80% of cardiac events can be prevented. With the AHA’s Check Change Control program, individuals can access valuable resources to successfully manage their blood pressure and potentially prevent heart disease.

In April 2018, dozens of employees lent their support to community organization FIND Food Bank when they answered phones and worked in the warehouse of the DOHC sponsored FIND annual telethon. And in 2019, DOHC employees will further support the telethon with a virtual food drive.

In March, DOHC provided a delivery van for the Mizell Senior Center’s Meals on Wheels program, which provides more than 120,000 meals to frail and homebound seniors every year.

Throughout the year, DOHC engages with numerous other sponsorships to help support the health and wellness of seniors, Hispanic and LGBTQ communities, as well as families in the Coachella Valley and surrounding high desert communities. But community support is not merely showing up at a fundraiser or walking for a cause. Every day, whether interacting with patients or fellow co-workers, DOHC employees practice “Language of Caring” skills that demonstrate their commitment to and appreciation for their neighbors and the communities they serve.

To express their immense gratitude to their employees, DOHC recently installed a 6’ x 15’ banner in the courtyard of the main campus with a sentiment that echoes the standard of excellent service the organization strives to reach daily: “Treat employees like they make a difference and they will.”
Increased Visibility Inspires Membership and Engagement

The Open Enrollment Period (OEP) is an important time of year for all of our affiliates across Southern California. OEP allows us the opportunity to make a positive impact on the communities we serve by sharing vital information about the quality of care and service we provide. Success requires a great deal of effort, collaboration, and partnership amongst brokers, medical group staff, physicians and other team members. Increasing visibility and encouraging participation through community engagement activities are some of the ways various groups impact membership growth and retention.

During the 2018 OEP, Heritage Sierra Medical Group (HSMG) successfully launched a commercial video to highlight the doctors and services they offer to the community. The video aired in the Antelope Valley Mall theater to capture the attention of captive audiences who may be interested in finding a new primary care physician in their area as well as those wanting to learn more about the healthcare services that are available to them and their family at HSMG.

After the commercials aired, four individuals walked into the Palmdale clinic location to enroll and become new Medicare Advantage members. Two of the members were Mr. and Mrs. Richardson, who were former Kaiser...
members. They first heard about HSMG through their Humana agent, Alex Salas-Manzo. Alex reviewed their current plan and communicated the savings they would receive by being members of HSMG and by enrolling into a Medicare Advantage Plan.

Soon after their enrollment, the Richardsons scheduled an appointment with their primary care physician, Dr. Regal and ADOC Medical Groups’ South Community Engagement Team were recently awarded certificates from Congressman Lou Correa and the House of Representatives honoring their service to the Community Health Initiative of Orange County (CHI OC). CHI OC helps the underserved population in Orange County by finding assistance and programs that improve daily living conditions and enhance quality of life. Regal and ADOC work closely with CHI OC to help provide members with important information, such as how to find physicians and other healthcare resources. Regal and ADOC also host healthy living classes and cooking demonstrations through CHI OC to help educate the community on how to stay healthy and better manage chronic disease.

After the commercials aired, four individuals walked into the Palmdale clinic location to enroll and become new Medicare Advantage members. Carmel Ernest. “I’m very satisfied with the overall experience that I received from my Humana agent and the whole team at Heritage Sierra Medical Group. My husband and I are building a new relationship with Dr. Ernest. I would absolutely recommend Heritage Sierra to others looking to find a new doctor and medical group,” added Mrs. Richardson.
New York HealthCare Partners, IPA’s Philanthropic Efforts Bring Joy to Many in Need

Heritage Provider Network affiliate HealthCare Partners, IPA of New York (not to be confused with HCP of Southern California) has a longstanding history of being engaged in community service and supporting initiatives that care for individuals in need. Their level of commitment inspired the organization to form the Employee Activities Committee in 2017, whose focus is to identify causes that need support – and together with other team members they help to gather donations, collect supplies and raise awareness of issues affecting the community they serve.

The spirit of the HealthCare Partners, IPA of New York (HCP-IPA) team has been infectious as their events grow bigger and better, the result of which has generated an even greater impact on the recipients of their efforts. The staff also experiences gratitude and pride in the company’s philanthropic approach to caring for community members and supporting the compassionate work of partnering with various charitable organizations.

NOTABLE CHARITIES IN 2018

Department of Social Services – Adopt A Family
HCP-IPA was matched with a family of 5, a mother with 4 children between the ages of 3-8 years old. Through their giving tree and basket raffles, more than $2,000 was raised which provided the family with a new bunk bed, clothes, toys for the children as well as gift cards to local stores.

Making Strides Against Breast Cancer
The HCP-IPA team gathered together for a number of fundraising events to raise more than $4,000 for the American Cancer Society. The team had a great time at their successful Flapjack Pancake Breakfast, selling more than 100 tickets to raise money to increase breast cancer awareness.

Sunrise Day Camp
The HCP-IPA staff laughed together at a comedy event held to raise funds for the world’s first full summer day camp for children with cancer and their siblings, provided completely free of
charge. More than $1,750 was donated to the Sunrise Association, whose mission is to bring back the joys of childhood to children with cancer.

**American Red Cross**
At least once a year, employees donate blood during the annual blood drive. In addition, HCP-IPA helps to support hurricane relief efforts by supplying non-perishable foods, clothing and toiletries.

**Marcum Workplace Challenge**
More than 100 employees raced to the finish line during Marcum – a 3.5 mile run/walk for charity. The raised funds are distributed among Long Island non-profits for children and animals.

**Additional Charities HCP-IPA Supported in 2018**
- John Thiessens Children’s Foundation
- Back to School Supply Drive
- American Heart Association
- ALS Association
- Saint Baldrick’s Foundation for Pediatric Cancer
- Autism Speaks – Autism Awareness
- Little Shelter Animal Rescue & Adoption Center
- Island Harvest Food Drive
- New York Blood Center
- Red Nose Day (to end childhood poverty)
Throughout the year, BFMC’s dedicated staff stays active in the community by teaming up to support various community events, which include Campout for Cancer, American Heart Association’s Heart and Stroke Walk, Out of Darkness Walk (suicide prevention awareness), American Cancer Society’s Making Strides Against Breast Cancer, and Hoffman Hospice’s Run to Remember.

During the holiday season, the staff partners with local organizations to bring some extra holiday cheer to the local senior community. BFMC is a platinum sponsor of Christmas for Seniors of Kern County, a program that collects sundries and gifts throughout the holiday season to provide to low-income, homebound seniors in Kern County. BFMC also collaborates with a local news station for the day-long annual “Stuff the Bus” event, during which they collect hygiene items donated by local residents to add to the Christmas for Seniors gifts.

Bakersfield Family Medical Center/Heritage Physician Network (BFMC/HPN) proudly celebrated 35 years of providing excellent medical care to the Kern County community.
Heritage Provider Network and Crain’s New York Business, Custom Division, Announce Nominations for the

Fourth Annual Heritage Healthcare Innovation Awards in New York

Heritage Provider Network (HPN), one of the nation’s leading physician-led managed care organizations, announced that nominations are open for the fourth annual Heritage Healthcare Innovation Awards. The awards, which are presented with Crain's Custom, a brand story-telling division of Crain’s New York Business, will showcase innovators who have most improved the access to and quality of affordable healthcare in the communities they serve in the greater New York area.

“Recognizing and honoring extraordinary healthcare innovation and rising healthcare stars throughout the New York metropolitan area for a fourth year promises opportunities for us at HPN and Crain’s New York Business to once again share significant insights and groundbreaking healthcare advances with all New Yorkers,” said Dr. Richard Merkin, Founder and CEO of HPN.

"It’s an honor to present the Heritage Healthcare Innovation Awards for the fourth year," said Mary Kramer, Group Publisher for Crain’s New York Business. "If past honorees are any measure, this year’s awardees will have the potential to benefit millions of New Yorkers.”

“Leadership, a passion for better, a sense of urgency, tell me why not, and do it now. This is what you see from New York nominees and winners, large and small, in the Heritage Healthcare Innovation Awards. These people and organizations refuse to be satisfied with the status quo, creating real solutions to improve healthcare and cost for thousands of New Yorkers when they need that help the most,” said Mark Wagar, President, Heritage Medical Systems.

“If past honorees are any measure, this year’s awardees will have the potential to benefit millions of New Yorkers.”

~ Mary Kramer, Group Publisher for Crain’s New York Business
Since 2016, Heritage Provider Network and Crain's Custom have honored more than 60 individuals and organizations, many of whom have gone on to make a significant impact on improving healthcare in their communities. Gil Addo, CEO and co-founder of RubiconMD and a 2017 award winner, expanded into California through a direct investment from the Heritage Provider Network and recently raised $13.8 million from additional investors.

Watch Gil Addo share about his experience on being a Heritage Healthcare Innovation Award winner: https://youtu.be/gSN8KmB1sIw

Matt Loper, CEO and co-founder of Wellth and a 2018 winner, announced his company raised $5.1 million in September for additional expansion and Call9, whose CEO Tim Peck also won in 2018, grew its outreach into two new markets in New York since winning, delivering life-changing care to thousands of patients.

**Winners will be awarded in the following five categories:**

**Heritage Innovation in Healthcare Delivery Award**
Recognizing an innovator in the development of new modes of diagnosis, treatment, and care who actively improves access to services, and improves the quality of healthcare overall.

**Heritage Research Investigators in Translational Medicine Award**
Awarded to an individual or team based on the most significant quantitative results achieved by accelerating the transition of novel and innovative diagnostic tools and treatments to patients.

**Heritage Healthcare Leadership Award**
Recognizing a leader in the New York area that has demonstrated significant impact in their healthcare field. This forward-thinker has forever changed the way care systems work through new models, processes, and pathways.

**Heritage Healthcare Organizational Leadership Award**
Honoring an organization that has fundamentally changed how healthcare is delivered. This organization has created or championed new ways of thinking and doing, uniting diverse constituencies to work together.

**Heritage Innovators in Healthcare Award**
Highlighting cutting edge applications of technology and up-and-comers in the healthcare industry. These breakthrough innovators are making significant contributions in the areas of technology, research, or new approaches to healthcare systems.

Nominations will be accepted beginning January 14, 2019 and ending at midnight March 30, 2019, at crainsnewyork.com. The online entry point is at crainsnewyork.com/heritage.

Finalists will be announced in April 2019 and winners will be revealed at a luncheon event in New York City on May 20, 2019. See last year’s event at: https://www.youtube.com/watch?v=La0ncMOFHJA

“**These people and organizations refuse to be satisfied with the status quo, creating real solutions to improve healthcare and cost for thousands of New Yorkers when they need that help the most.**”

~ Mark Wagar, President, Heritage Medical Systems
# Heritage Provider Network

## Affiliated Medical Groups

**THE LARGEST INTEGRATED PHYSICIAN-LED MEDICAL GROUP NATIONALLY**

For more than 40 years, HPN has provided quality, cost-effective healthcare to the communities we serve. Today, HPN and its affiliates manage the healthcare of more than one million individuals. Our network has thousands of primary care physicians and specialists and hundreds of hospitals.

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<th>Medical Group</th>
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<td>ADOC Medical Group</td>
<td><a href="http://www.adoc.us">www.adoc.us</a></td>
<td>800-747-2362</td>
<td>600 City Parkway West, Suite 400 Orange, CA 92868</td>
<td>Central and North Orange County</td>
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<td>Arizona Priority Care (AZPC)</td>
<td><a href="http://www.azprioritycare.com">www.azprioritycare.com</a></td>
<td>480-499-8700</td>
<td>585 N. Juniper Dr., Suite 200 Chandler, AZ 85226</td>
<td>Maricopa County and areas of Pinal County (Casa Grande Area)</td>
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<tr>
<td>Bakersfield Family Medical Center</td>
<td><a href="http://www.bfmc.com">www.bfmc.com</a></td>
<td>661-327-4411</td>
<td>4580 California Ave. Bakersfield, CA 93309</td>
<td>All of Kern County</td>
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<tr>
<td>Coastal Communities Physician Network</td>
<td><a href="http://www.ccphpn.com">www.ccphpn.com</a></td>
<td>800-604-8752</td>
<td>1305 Marsh St. San Luis Obispo, CA 93401</td>
<td>Arroyo Grand, Atascadero, Los Osos, Morro Bay, Paso Robles, Pismo Beach, San Luis Obispo, Templeton and Tulare</td>
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<td>HealthCare Partners, IPA</td>
<td><a href="http://www.hcchipa.com">www.hcchipa.com</a></td>
<td>516-746-2200</td>
<td>501 Franklin Ave. Garden City, NY 11530</td>
<td>Manhattan, Queens, Bronx, Brooklyn, Nassau, Suffolk, Westchester</td>
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<tr>
<td>Heritage Colorado Care</td>
<td></td>
<td></td>
<td>970-704-5368</td>
<td>2020 North 12th St. Grand Junction, CO 81501</td>
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<td>Heritage New York Medical, P.C.</td>
<td></td>
<td></td>
<td>516-531-2001</td>
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<td>Heritage Sierra Medical Group</td>
<td><a href="http://www.sierramedicalgroup.com">www.sierramedicalgroup.com</a></td>
<td>661-945-9411</td>
<td>44469 N. 10th Street West Lancaster, CA 93534</td>
<td>Kern, Los Angeles, and San Bernardino</td>
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<td>High Desert Medical Group</td>
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<td>43839 N. 15th Street West Lancaster, CA 93534</td>
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<td>Regal Medical Group</td>
<td><a href="http://www.regalmed.com">www.regalmed.com</a></td>
<td>866-654-3471</td>
<td>8510 Balboa Blvd., Suite 150 Northridge, CA 91325</td>
<td>Los Angeles, Orange, Riverside, San Bernardino, San Diego, and Ventura</td>
</tr>
<tr>
<td>Heritage Victor Valley Medical Group</td>
<td><a href="http://www.hvvmg.com">www.hvvmg.com</a></td>
<td>760-245-4747</td>
<td>12370 Hesperia Rd., Suite 6 Victorville, CA 92395</td>
<td>Los Angeles and San Bernardino</td>
</tr>
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Our Awards

Recognition of Commitment and Excellence

The recognition we have received demonstrates our practices in excellence. We’re proud to be awarded for our commitment to our members and our community.

Wellness Excellence Award in Health Education – Southern California Foundation for Health Care

Top Ten Physician Medical Networks in California by America’s Physician Groups

NCQA Certification for Credentialing

Elite Status of Excellence for the Standards of Medical Care by America’s Physician Groups

Recognized by the Integrated Healthcare Association (IHA) for our diabetic registries