CONNECTED COMBINATION PRODUCTS: PAST, PRESENT & FUTURE

By Napoleon Monroe, with supporting author Guy Furness

THE PAST: THROUGH CHANGING TERMINOLOGY & ADVANCING TECHNOLOGIES

In the first part of this article I would like to show that Connected Health has not suddenly emerged out of nowhere but, rather, how it has been (often quietly) developing and evolving over many decades, even centuries. Over the years, various approaches have been used across a wide range of applications, and a number of terms have arisen that describe and define a situation where, essentially, healthcare is being delivered and managed by one person or group of people to the recipient, but the person receiving the care is not in the same vicinity as the person or people providing and overseeing that treatment.

Perhaps the broadest term is telemedicine. In its early manifestations, African villagers used smoke signals to warn people to stay away from the village in case of serious disease. In the early 1900s, people living in remote areas of Australia used two-way radios, powered by a dynamo driven by a set of bicycle pedals, to communicate with the Royal Flying Doctor Service of Australia.[1]

Definitions of telemedicine differ. Some, such as that given by the WHO, include all aspects of healthcare including preventive care: "The delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities."[2] The American Telemedicine Association uses the terms telemedicine and telehealth interchangeably although it acknowledges that telehealth is sometimes used more broadly for remote health not involving active clinical treatments. Its definition is: "The use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. Telemedicine includes a growing variety of applications and services using two-way video, email, smart phones, wireless tools and other forms of telecommunications technology."[3]

> "The potential for consumer products using communications technology was enhanced by the development of many technologies: the internet; ever smarter phones with digital cameras and geo location; low-cost processing power; miniature, ruggedised sensors; small long-life batteries; app development tools: big data; cloud storage; numerous standards; encryption capabilities; and other technologies."

The first interactive telemedicine system, operating over standard telephone lines, designed to remotely diagnose and treat patients requiring cardiac resuscitation (defibrillation), was launched in 1989 by MedPhone Corporation (Paramus, NJ, US). A year later it introduced a mobile cellular version, the MDPhone. Twelve hospitals in the US served as receiving and treatment centers.[1]

Earlier still, in 1977, Dr Stanley Sarnoff invented and patented a mobile analog cardiac monitoring system.[4] That was

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preceded by his filings as early as July 1970. This early telemedicine product anticipated the future of telemedicine.

An interesting early link between telemedicine and the drug delivery space emerges at this point in the story because Stanley Sarnoff became most famous not for his cardiac remote monitoring products, but for an earlier achievement – the invention and manufacture of the first prefilled auto injector. US Patent 2832330 was granted on April 28, 1958 for the AtroPen, which contained atropine for self-administration in the event of nerve agent poisoning. This was the first drug delivery combination product.

Continuing development of auto injectors, Sarnoff followed the suggestion of a pioneering allergist, Dr Stephen Lockey Sr, and asked his engineering team to modify an injector to deliver epinephrine. This eventually led to the life-saving EpiPen, the most famous invention of Survival Technology, Inc, the company Stan Sarnoff founded, now owned by Pfizer. Today the EpiPen remains incredibly successful. It is, by quite some margin, the leading product in its category and, in 2015, became US distributor Mylan's first billion dollar product. The EpiPen was also the reason for a recent induction into the US National Inventors' Hall of Fame. Sheldon Kaplan, one of the engineers on Sarnoff's team, was posthumously inducted this year. While Kaplan's contributions were significant, like most great technology innovations, the development of EpiPen was very much a team effort. Three other people were named on the Kaplan patent cited by the National Inventors' Hall of Fame and there were other patents on the device. Also, suppliers pushed the limits of their technologies to make required components.

eHealth is another related term, used particularly in the UK and Europe, as an umbrella term that includes telehealth, electronic medical records, and other components of health information technology.

With the arrival of mobile phones came mHealth, an abbreviation for mobile health, the practice of medicine and public health supported by mobile devices. The term is most commonly used with reference to mobile communication devices, such as mobile phones and tablets, for health services and information, but also to affect emotional states. The mHealth field has emerged as a sub-segment of eHealth, the use of information and communication technology

Figure 1: The elements of a typical connected drug delivery device system. (Image courtesy New Directions Technology Consulting, LLC. Design by Kelly Barkhurst/smartpr.)

(ICT), such as computers, mobile phones, communications satellite, patient monitors, etc, for health services and information. mHealth applications include the use of mobile devices in collecting community and clinical health data, delivery of healthcare information to practitioners, researchers, and patients, real-time monitoring of patient vital signs, and direct provision of care (via mobile telemedicine).[1]

The potential for consumer products using communications technology was enhanced by the development of many technologies: the internet; ever smarter phones with digital cameras and geo location; low-cost processing power; miniature, ruggedised sensors; small long-life batteries; app development tools: big data; cloud storage; numerous standards; encryption capabilities; and other technologies.

Most recently, came standardised automated identity and data capture. Having these technologies available at reasonable cost provides capabilities for managing the internet of medical things. These technologies are now bundled together into connected healthcare devices. First came monitoring and diagnostic devices. Now we have moved on to connected combination products for remote monitoring and logging of drug delivery. These are sometimes called medication therapy management devices or medication telemanagement devices.

THE PRESENT

It is recognised that patients often do not follow directions. This leads to concerns about medication adherence (picking up the script/buying the medications), medication compliance (following the prescribed dosing regimen) and medication management (the two above and following all administration, storage and disposal directions).

Nerve agent antidote and epinephrine for treating anaphylaxis were the beginning points for combination products, but the drivers for the recent growth of connected combination products are based upon the following factors:

- The emergence and growth of the bio-technology/specialty drug industry
- Biotech products are often fragile and cannot survive the digestive system and first metabolic pass therefore parenteral administraton is required

Figure 2: Veta smart cases for each EpiPen® the patient (or their parents) need to track will work together with the app as an integrated system. (Image courtesy Aterica, Inc.)

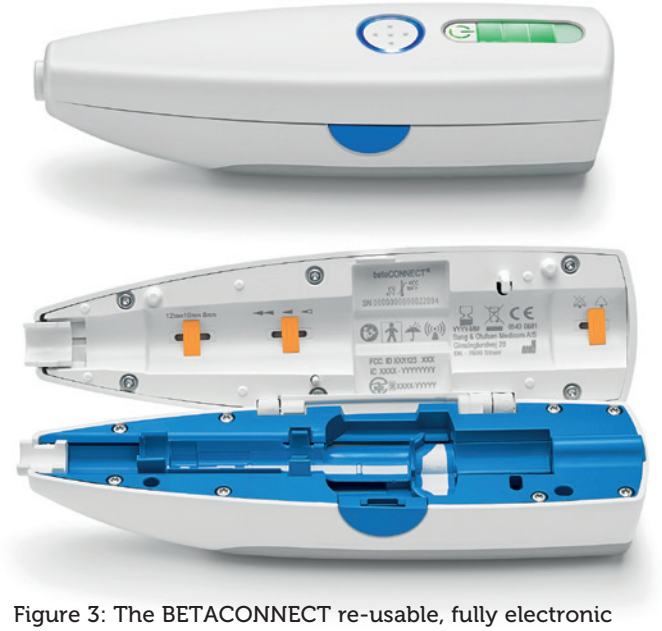

Figure 3: The BETACONNECT re-usable, fully electronic auto-injector can be used as part of a complete software-based system designed to track injection history and share important treatment information with healthcare providers. (Image courtesy of Bayer.)

- Specialty drug products often require special handling
- Desirability of administering drugs wherever the patient can conveniently dose (ie at home is preferable to hospital and primary care settings)
- Patient compliance with treatment regimens is poor
- Payment and procurement models have changed and will change more
- Stakeholders are demanding real world evidence regarding performance
- Human factors are recognised to be highly important for patient self-administered products…
- …Therefore, training and patient support are highly important, and
- Pharma has now recognised the value of connected combination products.

The essential elements of a system surrounding a connected combination product are shown in Figure 1. The claims made will determine whether a product is a combination product from a regulatory perspective.

There are numerous dosage forms under development with connected dispensers and delivery systems. This issue of ONdrugDelivery Magazine features connected devices for:

- Oral dosage forms (Balda Healthcare, Page 44)
- Inhalers (Biocorp, Page 20; and Adherium, Page 32)
- Re-usable and disposal auto injectors (Biocorp, Page 20; Medicom, Page 52; SHL Group, Page 38; and Ypsomed, Page 56)
- Wearable, large-volume injectors (Enable Injections, Page 12; West Pharmaceutical Services, Page 48; and Ypsomed, Page 56).

The examples that follow here provide an additional selection and represent only a fraction of the products already available or in development and heading towards the market.

AUTO-INJECTION

Veta™ Smart Case

Aterica, Inc (Waterloo, ON, Canada) has developed Veta™, a Bluetooth® Smart-connected case for the EpiPen, which is due to reach the market imminently. The case is transparent with sensors and electronics to monitor and communicate. Functionality, via the app, includes: locating a misplaced device; separation alerts; auto-injector removal from case alerts; temperature monitoring; expiry reminders; and connecting with patient-defined support circles which can include a private support circle (for example, parents, close friends, caregivers) and extended support circle (such as teachers, coaches). The patient determines how much or how little information about their location and daily habits each circle's members receive.

Veta can support up to eight EpiPen auto-injectors within the patient's network simultaneously meaning that Veta smart cases for each EpiPen the patient (or their parents) need to track will work together with the app as an integrated system, managing each auto-injector (see Figure 2).

Bayer BETACONNECT™

In 2014, Bayer Healthcare (Leverkusen, Germany) launched the first and, to date, only fully electronic auto injector, for its multiple sclerosis product, Betaferon (interferon beta-1b). The BETACONNECT auto injector (Figure 3), which was developed and is manufactured by Medicom Innovation Partner (Struer, Denmark; now part of Phillips-Medisize), can be used both independently (not connected) and as part of a complete software-based system designed to track injection history and share important treatment information with healthcare providers.

An app, called myBETAapp™ provides Bluetooth or USB connectivity and automated uploading of injection data and also allows patients to record other injection and general health information. Users will be able to connect electronically across multiple platforms (Windows, Apple Mac OS X, iOS, Android) to provide continuous feedback and notifications to help Betaferon® patients achieve and maintain their treatment goals. Patients can choose to share information via the myBETAapp™ dashboard with healthcare providers.

GrowJector® 2

Panasonic (Osaka, Japan) and JCR Pharmaceuticals (Hyogo, Japan) collaborated on the development of a connected digital auto injector for human growth hormone (hGH), which won the 2012 "Good Design Award" sponsored by the Japan Institute of Design Promotion. The device, called GrowJector 2, has data-logging and communications capabilities. Panasonic has worked on other versions of the device for other companies' products.

Unilife's LISA™

The LISA platform of smart disposable auto-injectors (Figure 4) from Unilife Corporation (York, PA, US) allows a range of ergonomic shapes and sizes and a series of options that can be tailored to the specific needs of an individual therapy and its target patient population. Options include the heating of the molecule to room temperate prior to an injection, the ability for a patient to control the speed or depth of each injection, and the pairing of the device with Bluetooth LE connectivity as well as a related app. The LISA connected injector platform has attracted various multinational pharma partners.

INHALATION

Propeller Health

Propeller Health (Madison, WI, US) is developing an add-on with associated app, which connects asthma and COPD inhalers (MDIs, DPIs and others) and has already partnered with GlaxoSmithKline (Brentford, UK) and Vectura (Chippenham, UK), amongst others.

The process of using Propeller's device, from the use point-of-view, is straightforward. They sign-up online / download the app, the Propeller device ships immediately and arrives within days, the patient attaches it to their inhaler and then continues using their device as normal. The app is designed to "learn" and the company intends that patients using the product's mobile apps, desktop web apps and messaging and notification tools gain insights into their triggers, reduce the hassle of managing their asthma or COPD, and become better connected (in terms of their disease management) with their care team (including family members and healthcare professionals). For the healthcare professional, Propeller says it helps focus on patients most in need of attention, increasing efficiency through smart notifications, a patient dashboard and communication tools.

The company has developed a body of evidence, and published substantial trial data, including in peer-reviewed journals, linking the use of their connected product with increases in inhaler adherence and compliance and, going further, suggesting a causal link between the use of their connected product and significant improvements in disease outcomes. For example, earlier in 2016, results were published of a 12-month, randomised, controlled clinical trial conducted by Dignity Health (San Francisco, CA, US) investigating short-acting beta agonist (SABA) use in 495 asthmatics. The paper concluded that, compared with the control group which received routine care without the connectivity of the Propeller platform, "the study arm monitoring SABA use with the Propeller Health system significantly decreased SABA use, increased SABA-free days, and improved ACT scores (the latter among adults initially lacking asthma control).[5]

> "FDA believes that providing patients with access to accurate, useable information about their healthcare when they request it (including the medical products they use and patient-specific information these products generate) will empower patients to be more engaged with their healthcare providers in making sound medical decisions."

Figure 4: Unilife's LISA™ platform of smart disposable auto injectors allows pairing of the device with Bluetooth LE connectivity as well as a related app.

Figure 5: The eMDI from Presspart and Cohero.

Cohero and Presspart

Partners Cohero Health (New York, NY, US) and H&T Presspart (Blackburn, UK) have developed a connected metered-dose inhaler, eMDI (Figure 5) which incorporates electronics to track and communicate medication utilisation passively. A sensor records the date and time medication is actuated, which is then stored in onboard memory, as well as shared wirelessly via Bluetooth. It works seamlessly with Cohero Health's platform of connected devices and mobile applications, which actively engage and empower respiratory patients by tracking medication adherence and measuring lung function. The companies announced the completion of their device in April 2016, making it available to pharmaceutical industry partners.

Cohero has numerous partnerships and announced a US$2 million (£1.4 million) seed financing in December 2015.

Qualcomm Life / Novartis

In early 2016, Qualcomm Life partnered with Novartis on the development of a connected version of Novartis' Breezehaler™ inhaler, which is used to deliver the company's COPD products Onbrez (indacaterol maleate), Seebri (glycopyrronium bromide) and Ultibio (indacaterol + glycopyrronium).

With launch of the next-generation, connected Breezehaler planned for 2019, Novartis aims to be the first company in respiratory medicine to offer "a completely integrated, connected delivery device to provide a seamless, easy to use and simple experience for patients".

A small, disposable, low power module contained within the inhaler detects and reports usage, the time that the inhaler is used, as well as additional relevant information for patients and physicians. The module then wirelessly sends the data to the patient's smartphone and a Novartis COPD mobile app, which sends the data to the cloud, allowing patients and potentially their healthcare providers to monitor their COPD.

Qualcomm Life, a subsidiary of chip-maker Qualcomm, is to develop the design for the module containing the connectivity tech. Qualcomm Life is a very active player in the connected health sector, with numerous initiatives and partnerships with hospitals, pharma companies and other organisations (see Qualcomm Life's article in this issue, Page 27).

ORAL SOLIDS, SMART PILLS & PACKAGING

Proteus / Discover

Probably the most publicised company developing connected tech for oral delivery is Proteus Digital Health (Redwood City, CA, US). The company's platform (Figure 6) comprises four elements: sensor-enabled pills, containing an ingestion sensor the size of a grain of sand; a body-worn patch which receives a signal from the pill when it reaches the stomach; monitors patient activity and rest patterns, and communicates with the cloud relaying information to the patient's smartphone and, with their permission, to their doctors too; the Discover App, which enables patients to keep track of their medications, steps, activity, rest, heart-rate, blood pressure and weight, set multiple medication taking schedules and receive reminders; and the Discover portal, which allows doctors access to patient data helping them allocate resources to those who need them most and optimise tailored treatment decisions for each patient.

Figure 6: The Proteus platform comprises four elements: sensor-enabled pills, containing an ingestion sensor; body-worn patch (pictured) which receives a signal from the pill; the Discover App (pictured); and the Discover portal, for physicians. (Image courtesy Proteus Digital Health.)

Like Propeller Health in the inhalables sector as previously mentioned, in the oral delivery sector Proteus is building a body of robust evidence to support its claims that its platform improves clinical outcomes. Most recently, at the 65th Annual American College of Cardiology meeting in Chicago, IL, US, in April 2016, the company reported interim results from a randomised, controlled clinical trial in 96 patients with uncontrolled hypertension and type-2 diabetes, which revealed that patients who used Proteus Discover achieved statistically greater reduction in blood pressure and low-density lipoprotein cholesterol, known risk factors for cardiovascular events, and were more likely to achieve their blood pressure goal compared with those receiving usual care.

IMC Med-ic

The smart blister pack, Med-ic, from Information Mediary Corporation (Ottawa, ON, Canada), utilises a CPU and attached printed sensor grid embedded in the blister package (Figure 7). The CPU records the time when a given tablet or capsule is expelled from its blister, and stores the data for later display and/or analysis.

At the time of refilling the prescription or during a clinical trial follow-up visit, the patient's compliance data are downloaded to a PC via a CertiScan® RFID Reader, or downloaded using any NFC-enabled

Figure 7: Med-ic smart blister pack utilises a printed sensor grid embedded in the blister package to record when a given tablet or capsule is expelled from its blister. (Image courtesy IMC.)

smart phone or tablet. CertiScan Software displays the information immediately on a PC using an intuitive graphic interface featuring point-and-click, drill-down capabilities ranging from daily to annual at-a-glance views. Using an NFC-enabled smart phone or tablet, compliance data can similarly be displayed directly on the device. The software extends electronic record compliance with 21 CFR Part 11 back directly to the patient source.

No patient information is stored on the CPU, ensuring confidentiality. CPU-resident data comprise simply a sequence of numbers representing time-events that can only be related to a patient when the study code is broken by the sponsor. Inputting compliance data collected by the traditional methods of patient reports, medication diaries and pill counts is costly. Med-ic eliminates the need for the double entry compliance data phase, dramatically reducing data entry costs while offering researchers the most reliable and valid records of patient adherence to the study regimen.

West Rock's Smart Packaging

WestRock (Norcross, GA, US), which was formed in 2015 from a combination of MeadWestvaco and RockTenn, is developing a range of connected smart packaging for oral dosage forms. MEMSCap for example, is a connected, child-resistant cap with integrated circuits that fits most standard pill vial sizes and can record up to 3,800 dosing events (Figure 8).

Figure 8: MEMSCap is a connected, child-resistant cap with integrated circuits that fits most standard pill vial sizes. (Image courtesy of WestRock.)

Whilst MEMSCap works on the assumption that a pill is removed each time the container is opened, other WestRock products can detect when individual pills or capsules are removed from blister packaging. CarePak features a tiny, hidden microprocessor and printed, conductive inks which record the date, time and location of each pill removed from the package. Tracking the removal of each specific tablet is critical for dose titration (pill dosage changes) and for regimens with a mix of placebo and active drugs.

Dispensers and Pouches

Many companies are now developing smart pill dispensers and organisers. Vitality Health (Los Angeles, CA, US), for example, was an early introducer of smart pharmaceutical packaging and has developed a pill vial cap (along the same lines as MEMSCap described above) called GlowCap. It is also developing a smart, resealable pouch, GlowPack, which can hold oral solids (including blister packs), injectables, inhalers, drinkables, and topical ointments. It provides both visual and audible reminders, glowing at dosing time and glowing and playing a melody one hour past dosage. It includes an automated reminder call to the patient two hours past missed dosage. The device communicates via an AT&T wireless cellular connection and allows for detailed weekly and monthly reporting to patient, clinician and manufacturer.

THE FUTURE OF CONNECTED COMBINATION PRODUCTS

As can be seen from the small sample of projects and products described here, and elsewhere in this issue, many well-informed stakeholders are funding the further development of connected combination products. Some are simple informational products which are not medical devices. Others combine state-of-the-art technologies. Future developments will utilise legacy and new technologies in ways beyond current dreams.

As with consumer products, to be successful, connected combination products should be simple to use and meet real needs. A May 2016 Wall Street Journal article entitled, "Smart Tampon? The Internet of Every Single Thing Must Be Stopped", cautioned that not every object should connect to our smartphones – and if it does, it should at least work. Whilst it described a number of so-called smart devices as actually being dumb, not smart – for example, the smart umbrella that reminds you not to leave it behind, or the smart tampon that reminds you when to change it – the article conceded that there were truly smart devices out there with real potential, and specifically mentioned medication telemanagement devices as serving real needs.[6]

In the coming months, market needs will drive individual stakeholders and their trade and professional associations to push towards reimbursement, resolving regulatory and security issues. Indeed as this article was going to press, the US FDA Center for Devices & Radiological Health (CDRH) issued a Draft Guidance for Industry entitled, "Dissemination of Patient-Specific Information from Devices by Device Manufacturers".[7] The fact of the draft guidance itself is telling and suggests that the regulators are coming up to speed on the benefits of engaging patients in their treatment by providing them with data.

The Draft Guidance says: "FDA is issuing this guidance to clarify that manufacturers may share patient-specific information recorded, stored, processed, retrieved, and/or derived from a medical device with the patient who is either treated or diagnosed with that specific device."

> "Pharma has now recognised the value of connected combination products."

It continues: "FDA believes that providing patients with access to accurate, useable information about their healthcare when they request it (including the medical products they use and patient-specific information these products generate) will empower patients to be more engaged with their healthcare providers in making sound medical decisions."

While the Draft Guidance suggests no additional regulation of devices regarding providing data to patients, industry should follow the development of this and other guidances, and be cautious about any labelling, which might be regulated.

In the near future, the value in connected combination products will be clearly demonstrated. As with consumer products, this will further stimulate demand. Partnering activity will increase because few, if any, stakeholder organisations have all the required capabilities in house. As with technology and consumer industries, firms will co-operate using shared IP to secure freedom to operate. They will acquire/license/cross license and co-operate to exclude infringers as elsewhere in these industries. Thus the sale and licensing of medication telemanagement IP will become strategically important.

As the market for connected combination products grows, new entrants will appear and challenge the early developers. For example, Chinese firm Delfu Medical (Changzhou City, Jiangsu Province, China) showcases a large range of electronic devices on its website including electronic syringes, auto injectors, insulin pumps and more.[8]

Service beyond the script and real world data will be used to extend pharmaceutical product life and reach. Stakeholders will enjoy revenue streams from new products/services grown from medication telemanagement, and pharma product service and support will improve pharma's stakeholder relations.

Developing countries will explore more creative uses of connected combination products. Just as with the smart phone and the internet, developing countries may enjoy greater benefits because they are not bound by legacy customs and systems. A number of US leading companies including Cardinal Health have already partnered with non-profit organisation Trek Medics International (New York, NY, US) which is dedicated to improving emergency medical systems in communities around the world without reliable access to emergency care. Imagine a connected drug kit with interactive instructional capabilities in the situation pictured in Figure 9.

Figure 9: The difficulties involved with delivering emergency care to a remote location in the developing world (Image courtesy Trek Medics)

The world is just waking up to the promise of connected health and specifically in drug delivery systems and other combination products. It is truly exciting to contemplate its full potential and what might be achieved by applying connectivity in healthcare over the coming years and on into the future.

ABOUT THE AUTHOR

Napoleon Monroe is Managing Director of New Directions Technology Consulting, LLC. His diversified background extends from developing and producing emergency pharmaceutical delivery systems to managing private brands for a Fortune 500 company, to building and managing the IP portfolio for a company that is now part of Pfizer. His expertise includes product development, licensing, regulatory processes, risk management and international marketing, with experience managing business relationships in more than 30 countries.

As Vice-President of Corporate Brand Development for global healthcare distribution and service company Henry Schein, Inc, Mr Monroe was responsible for all aspects of the company's private brands. He grew annual sales by more than 500% to more than US$500 million. While there, he also began filing medication telemanagement patents.

Before Henry Schein, Mr Monroe spent more than 20 years at Survival Technology (now the Meridian Medical Technologies division of Pfizer) where, as a Corporate Vice-President, he was responsible for product development and systems strategy. While at Survival, with colleagues he invented three medical devices that were patented and commercialised; two were for auto-injectors and one was for a transtelephonic, peak-flow monitoring device.

There, he also led teams that invented, prototyped, tested, commercialised and scaled-up such products as: the EpiPen, still the leading product for treatment of anaphylactic shock; the Antidote Treatment Nerve Agent Auto Injector delivery system, which still protects US and allied military and civilian personnel; and products that supported the formation of Shahal Medical Services in Israel (acquired by Shanghai Jiuchuan) and Raytel (now part of Philips in the US).

Mr Monroe has been cited in a number of industry publications. He is active in the Parenteral Drug Association, HIMSS, Prescription for a Healthy America, Health IT Now, National Defense Industrial Association and other groups. He is a longstanding member of the American Telemedicine Association. He supports East Carolina University where he did his undergraduate degree.

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