THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

JUL 24 2013

The Honorable Barbara A. Mikulski
Chairwoman
Committee on Appropriations
United States Senate
Washington, DC 20510

Dear Madam Chairwoman:

The enclosed report responds to the House Report 112-493, page 266, accompanying H.R. 5658, the Department of Defense (DoD) Appropriations Bill, 2013. The Committee requested that the Assistant Secretary of Defense for Health Affairs report on how DoD's peer review process for the Congressionally Directed Medical Research Programs (CDMRP) can be strengthened.

The CDMRP manages its research programs using its established and highly recognized management process. The CDMRP's program management is structured to re-evaluate its review processes as well as the state of the science on an annual basis. Proposed process enhancements for Fiscal Year 2013 to strengthen the program include implementing enhanced training specific to each award mechanism for all panel members, adding a descriptive paragraph for each review criterion in the critique template to ensure clarity of the critique, and providing staff access to the electronic peer review scoring system for real-time monitoring of critique narrative and score alignment. Future enhancements include implementation of high-definition database and analytic software for peer and portfolio review.

Thank you for your interest in the health and well-being of our Service members, veterans, and their families. A similar letter is being sent to the Chairman of the House Appropriations Committee.

Sincerely,

Jonathan Woodson, M.D.

Enclosure:
As stated

cc:
The Honorable Richard C. Shelby
Vice Chairman

THE ASSISTANT SECRETARY OF DEFENSE

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HEALTH AFFAIRS

JUL 24 2013

The Honorable Harold Rogers
Chairman
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

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Sincerely,

Jonathan Woodson, M.D.

Enclosure:
As stated

cc:
The Honorable Nita M. Lowey
Ranking Member

# REPORT TO THE CONGRESSIONAL DEFENSE COMMITTEES IN RESPONSE TO HOUSE APPROPRIATIONS COMMITTEE REPORT 112-493, PGS 265-266, ACCOMPANYING H.R. 5658, THE DEPARTMENT OF DEFENSE APPROPRIATIONS BILL, 2013

## "CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAM"


## SUBMITTED BY THE OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)

## SUPPORTED BY THE U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND, CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

The estimated cost of report or study for the Department of Defense is approximately $13,000 for the 2013 Fiscal Year. This includes $5,160 in expenses and $7,710 in DoD labor.

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# Congressionally Directed Medical Research Programs

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## BACKGROUND and PURPOSE OF REPORT

The Assistant Secretary of Defense for Health Affairs is requested by the House Appropriations Committee Report 112-493, page 266, to "submit a report to the House and Senate Appropriations Committees not later than 120 days after the enactment of the Act to the Congressional defense committees on how the Department of Defense's peer review process for the CDMRP can be strengthened." This report is being provided through the Intergovernmental Service Agreement with the U.S. Army Medical Research and Materiel Command (USAMRMC) and the Congressionally Directed Medical Research Programs (CDMRP).

As the program execution and management agent for these research programs, the CDMRP is responsible for planning, coordinating, integrating, and execution. The CDMRP's flexible execution and management cycle includes the receipt of annual Congressional appropriations, new research programs stakeholder's meeting, vision setting, release of funding opportunities soliciting research applications, pre-proposal screening and invitation to submit full applications, full application receipt and review, recommendation of grants for funding, and oversight of research grants. The achievements of the CDMRP can be attributed, in part, to continual process improvements. These processes have been refined over the past 20 years and are fine-tuned to meet each program's specific needs. The CDMRP has effectively and efficiently processed, reviewed, and supported research that is advancing science and improving the lives of Service members and the American public. These best business practices include:

> While these processes have proven to be efficient and effective, the CDMRP continually evaluates its processes to ensure that the most cost-effective process is used and to ensure that each program is addressing its vision and mission.

- "Out-of-the-box" thinking with support of innovative, high-impact research;
- Employing an innovative and rigorous application review process;
- Establishing and maintaining effective partnerships with all stakeholders;
- Sound stewardship using efficient and effective business processes to keep management costs low; and
- Program evaluation to examine the CDMRP processes and program accomplishments to ensure that the CDMRP is using the most effective processes, and that each program is addressing its vision and mission.

Each of the CDMRP's research programs is managed by a multi-disciplinary team. Each CDMRP program is guided by an advisory board (which is either an Integration Panel or Joint Programmatic Committee equivalent) comprised of consumers[1] from advocacy communities, scientists, members of the military, and clinicians with renowned expertise in the specific research. Each program has a vision/mission that is focused on ending or curing that disease, condition, or injury, ameliorating its consequences, or having a major impact on the quality of life of its survivors. On an annual basis, each advisory board defines its program's vision.

[1] The CDMRP defines consumers as patients, survivors, family members, or caregivers of people living with a disease, injury, or condition and are representatives of consumer advocacy, support, or military organizations.

Following a comprehensive review of the program's portfolio, the current research landscape, and potential directions, the investment strategy for the program is then developed. In Fiscal Year (FY) 2012, more than 290 scientists, clinicians, and consumers, which included Service members in all capacities, served on the advisory boards across 18 research programs. Establishment of the program's vision and investment strategy leads to the development of funding opportunities that describe the intent of each award mechanism to solicit research applications aimed at making a significant impact. Critical to ensuring that each of the CDMRP research portfolios reflects not only the most meritorious science, but also the most programmatically relevant research, is the two-tier review process, adopted from the recommendations set forth in 1993 by the National Academy of Science's Institute of Medicine.[1] Scientifically sound applications that best meet the program's interests and goals are recommended to the Commanding General, USAMRMC and the Assistant Secretary of Defense for Health Affairs, for funding. Once approved, funding notifications are sent to investigators; awards are made in the form of one- to five-year assistance agreements, and assigned to the CDMRP staff for full-cycle support of research and outcomes. The CDMRP ensures the integrity of the review process and provides transparency by making lists of funded applications, advisory board members, peer review panelists, and research accomplishments available to the public on the CDMRP Website (http://cdmrp.army.mil). The CDMRP programs are scientifically sound, innovative, and responsive to Congressional intent and the needs of the military and the public. The 1997 Institutes of Medicine report praised USAMRMC and the CDMRP, stating it was favorably impressed with the processes implemented by the CDMRP and supported its continuation.[2]

The current report provides a summary of the CDMRP's rigorous peer review processes, the types of innovative, high-impact research solicited for and funded efforts along the translational continuum and current and future strategies to further improve the peer review process.

## CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAM PEER REVIEW PROCESS: PROVEN BEST PRACTICES FOR FUNDING BIOMEDICAL RESEARCH

Since its inception, the CDMRP has focused on funding innovative, high-risk, high-reward research not typically supported by other funding agencies, as well as projects that forge new collaborations in furtherance of important research objectives. To facilitate this goal, the CDMRP developed robust processes for review of applications for funding. These processes and their ability to identify scientifically meritorious research that will best contribute to achieving the goals of each CDMRP research program, have been scrutinized and refined over two decades. This refinement, together with the unique tenets of the CDMRP application review[3] as originally designed, have led to a system of review lauded by Congress, the scientific and advocate communities, and held up as an example for other agencies and organizations.

To ensure both scientific excellence and programmatic relevance, the CDMRP administers a two-tier review process recommended by the Institute of Medicine.[1] Peer review, the first tier of review, is a criteria-based process in which applications are evaluated based on their individual scientific and technical merits in a given discipline, or combination of disciplines. Programmatic review, the second tier of review, is a comparison-based process in which applications of high scientific and technical merit from the array of disciplines compete in a common pool.

Programmatic reviewers do not automatically recommend funding for all submissions highly scored by scientific peer review panels. The applications that have the highest potential to help achieve the vision and goals of the respective program (programmatic relevance, relative innovation and impact respective to the award mechanism, portfolio balance, and adherence to the intent of the mechanism) are selected for funding. To be funded, an application must be favorably reviewed by both levels of the two-tier review system. In addition, for some award mechanisms (i.e., funding opportunities), a third step is included, where a pre-application screening process is used to focus resources, including those of the applicant, the reviewers, and the program, on proposed projects that best meet the intent of the award mechanism. Investigators of favorably reviewed pre-applications are then invited to submit full applications.

## FUNDING OPPORTUNITIES BY TYPE OF RESEARCH

Each of the CDMRP's research investment strategies is responsive to the dynamic changes in each respective field, and is adapted annually to meet emerging needs of patient and research communities, gaps in research, and other barriers to progress in curing, rehabilitating, or eliminating the disease(s), injury, or condition. The advisory board of each program makes recommendations that are implemented through specific and clearly defined award mechanisms developed to target needs, gaps, and research focus, and range from supporting simple concepts to more advanced research (clinical trials). The CDMRP has developed and released over 690 award mechanisms to the public as funding opportunities, for the solicitation of research applications focused on the specific needs of each research program.

The CDMRP has offered award mechanisms that support four types of research. Each award mechanism was assigned to one of the following:

- Basic research: Fundamental research for the generation of new ideas, knowledge, hypotheses, or preliminary data to support applied and more advanced research. Examples include "bench-science," and the development of animal models.
- Applied research: Research includes utilizing basic research findings to develop material and knowledge products to prevent, diagnose, or treat diseases/conditions/injuries. Examples include testing using animal models, animal validation, technology development, and clinical research without an intervention.
- Advanced research: Late-stage applied research, including testing and refinement of material and knowledge products in human subject populations. Examples include clinical research with an intervention, and clinical trials.
- Combination research: Research utilizing a variety of approaches including basic, applied, or advanced research. Award mechanisms that span across basic, applied, and advanced research fall into this category.

Table 1 depicts the award mechanisms offered by the CDMRP over the course of its lifetime (FY 1993-FY 2012). On average, the largest percent of all the CDMRP award mechanisms allocated in the investment strategies are in the categories of applied and combination research. On average, the percent of funding allocated in the investment strategies to support basic, applied, and advanced research is similar and does not reflect the differences in the number of

award mechanisms in each category. Over the lifetime of the CDMRP, the largest percent of all of the CDMRP research awards were made in the combination research category which includes basic, applied, and advanced research. The percent of basic research is generally funded using lower dollar award mechanisms in the range of $100,000 to $500,000; whereas, advanced research involving clinical trials requires more funding, typically in the $1 million (M) to $10M range. The similar funding allocations in the investment strategy and in the award funding for basic, applied, and advanced research strongly suggest that translational research is a priority for the CDMRP research programs.

**Table 1. Investment Strategy and Research Funded by Type of Research FY 1993 – FY 2012****

| Type of Research | % of Award Mechanisms Allocated in Investment Strategy | % of Funding Allocated In Investment Strategy | % of Research Awards | % of Award Funding |
|---|---|---|---|---|
| Basic | 23% | 10% | 36% | 11% |
| Applied | 33% | 9% | 5% | 11% |
| Advanced | 14% | 8% | 2% | 6% |
| Combination | 30% | 73% | 57% | 72% |

** FY 2012 awards are in negotiations and are not final.

For the individual CDMRP research programs, Appendix A shows the planned investment strategy in the left column compared to the research awards funded in the right column. The differences in investment strategy between programs are the result of several factors. Award mechanisms in the advanced research category (which includes clinical trials) may be limited due to the maturity of science in the specific disease or condition, limited availability of funds to support advanced research such as clinical trials, or strategic decisions based on program focus. In addition, research programs in less mature areas of research generally focus primarily on basic or applied research in efforts to fill gaps and create the foundations needed for more advanced research. Moreover, each CDMRP research program's investment strategy is defined on an annual basis to target the areas that are most critically in need of research.

The number of research awards made in each type of research over the lifetime of the individual CDMRP programs (Appendix A, right column) varies by program. Each research program's investment strategy is used as a guide when its advisory board recommends applications for funding; the number of awards recommended for funding within each award mechanism is dependent on the number and quality of applications, as well as the program relevance, relative innovation or impact, portfolio balance or composition, and adherence to the intent of the award mechanism.

Appendix B shows research funded (FY 2009-2011) by type of research. Each program managed by the CDMRP has a unique vision that targets the most critical aspect along the pipeline of translating research to the clinic.

## TRANSLATING CUTTING-EDGE BASIC RESEARCH INTO CLINICAL PRACTICE

In an era of rapid biomedical advancements, our increased ability to prevent, detect, and treat diseases, injuries, and medical conditions is providing patients with an array of therapeutic interventions and an overall better quality of life. While these advances have been extraordinary in moving medicine forward, the majority of conditions does not have a cure or cannot be prevented. Advanced research in the form of clinical trials is the engine that drives progress against disease by rigorously testing the safety and efficacy of new products and potential therapeutics in patients. However, prior to the translation of scientific findings into clinical trials, an increase in the basic understanding of key disease processes must occur and be substantiated. Therefore, success in translational medicine demands a continuous pipeline of basic research discoveries that can further potential clinical application.

Success in translational medicine demands a continuous pipeline of basic research discoveries that can further potential clinical application.

To maintain movement of promising basic and applied research along the translational research continuum, some of the CDMRP programs offer Expansion Awards. These Expansion Awards are open only to investigators previously funded under a specific award mechanism and provide support for the further development of innovative ideas. In contrast to other funding agencies that provide continuation or supplemental funding of ongoing research, Expansion Awards are competitive and undergo the CDMRP's rigorous two-tier review, and support further development of research that will impact the specific disease and patient care.

Many of the CDMRP-managed projects have the potential to become fielded products for Service members. The USAMRMC designed and implemented a process called Decision Gate to effectively manage medical product development in a cost-effective, consistent, and transparent process. Decision Gate, which is grounded in the DoD Directive 5000 series, FDA regulations, and best industry practices, allows the USAMRMC to remain responsive to the changing needs of Service members. Research products identified as having sufficient scientific maturity and potentially filling a documented Army need enter into Decision Gate. During the continued development of a research product, the product proceeds through a series of decision points (called Milestones) in which the Milestone Decision Authority decides whether product development continues as planned, continues with a revised plan, or development is terminated. The CDMRP has participated in the formation of several teams in the Decision Gate process that are working to improve transfusion safety and diagnosis and treatment of traumatic brain injury.

The CDMRP has enabled several investigators to bridge the gap between basic science, applied science, and medicine. An extensive list of over 65 CDMRP-funded research efforts currently in clinical trials or that have already been adopted as standard of care that were initiated as basic or applied early-phase clinical research can be found in Appendix C.

## CURRENT AND FUTURE STRATEGIES TO CONTINUE IMPROVING THE CDMRP REVIEW PROCESS

Many of the challenges involved in executing an efficient and effective review process for research proposals are shared by all funding agencies. However, since its inception in 1993, the CDMRP has developed and executed a number of processes designed to mitigate the human-derived variances in review, and provide the most consistent, fair, and thorough review possible for each of the thousands of pre-applications and applications received every year. Because each of the CDMRP programs and award mechanisms differ in intent and focus, the CDMRP tailors the review panels to fit the specific expertise required. Although some reviewers may participate from year to year, standing panels are not used by the CDMRP, which allows for the flexibility to adapt and focus reviewer expertise as needed. Specialty reviewers are employed to target important aspects of award mechanisms, such as consortia, drug or technology development, innovation, statistics, and clinical trials. Across all review panels, the CDMRP involves consumer advocate reviewers as representatives for each program area. The CDMRP was the first U.S. federal funding agency to include consumers on its review panels,[4] and to date, remains the only federal funding agency that includes consumers on every aspect of decision-making. Consumers play a major role in maintaining the focus of each program on relevant research that has the potential to have a significant impact on the community affected. The CDMRP specifically tailors detailed review criteria for each award mechanism, and those criteria are clearly outlined in the widely-available published funding opportunities. Reviewers at both tiers of review follow published criteria to direct their reviews. Peer reviewers are provided critique templates via an electronic peer review scoring system. Critiques and scores regarding the merits of an application are aligned directly with each review criterion. These critiques contain evaluative narratives of strengths and weaknesses for each review criterion, which provides detailed information to the investigators about the pertinent factors that, affected the outcome of their application's review.

The CDMRP tailors the review panels to fit the specific expertise required.

The CDMRP was the first U.S. federal funding agency to include consumers on its review panels, and to date, remains the only federal funding agency that includes consumers on every aspect of decision-making for the investment of program funds.

The CDMRP uses several approaches to evaluate and continue to improve its peer review processes:

**Approach: Conduct program analysis and evaluation.** The CDMRP continues to evaluate the effectiveness and efficiency of its review processes. Several analyses have focused on specific aspects of peer review, which have aided in making decisions on what is working well, and what can be improved. Prior projects have resulted in process improvements such as: incorporating blinding of study investigators and institutions at both tiers of review to focus on the merit of the proposed research; peer reviewer recruitment; the inquiry review process; expedited review in which applications are reviewed and scored as done for all applications, but are not discussed in

the peer review panel unless championed; online peer review for small dollar awards; and peer review scoring prior to and during peer review discussions.

The CDMRP recently analyzed its process for recruitment of scientific reviewers. The CDMRP's process currently involves assessment of each peer reviewer's expertise as noted by a common scientific code as well as reviewer's self-evaluation of their expertise on specific applications prior to assignment. The CDMRP is striving for greater precision in identifying reviewer expertise and recruiting reviewers whose expertise is most precisely aligned with the applications. This is particularly significant in the context of the CDMRP's practice of recruiting a new panel of reviewers based on the research foci of the applications that are received, rather than maintaining a standing panel of reviewers.

**Approach: Survey peer reviewer panel members.** At the conclusion of every peer review, the CDMRP surveys the peer reviewers to provide feedback on the process. These surveys include topics such as the leadership of the Scientific Review Officer and panel chairperson, clarity of the review criteria, effectiveness of the scoring system, and whether each application was given a fair and thorough evaluation. To monitor the robustness of the scientific reviews, each panel member is asked to what degree they feel the panel members had the appropriate expertise to review the applications, as well as the degree to which panel discussion contributed to the quality of the reviews. Actions taken as a result of the CDMRP's peer review survey have resulted in numerous process improvements over several years, including revisions to award mechanisms; aligning review criteria with required proposal components; adding categories of "strengths" and "weaknesses" for each review criterion in the critique template; and review panel recruitment. The CDMRP will continue to seek feedback from its peer review partners and implement process improvements for a robust peer review.

Through continued process improvements enabling funding of research efforts in all phases of the translational pipeline, and supporting investigators to pursue transformative research, the outcomes of the CDMRP-funded research has a high probability to make clinical and translational research advances.

**Approach: Conduct workshops.** The CDMRP conducts an internal workshop on an annual basis, in which specific areas or items for improvement are brainstormed and discussed among the CDMRP directors, program managers, and support contractors. The CDMRP review processes are often compared and contrasted with those of other funding agencies to ensure that the CDMRP processes are using current best practices for application review. Action items following the workshops are prioritized for follow-up and implementation during the current fiscal year. Several improvements have resulted from this self-monitoring approach, including format, content, and quality control of peer review critiques; quality assurance of peer reviewer critiques; webinar training for the Scientific Review Officer, panel chair, and peer reviewers; and complementing online reviews with Scientific Review Officer-moderated online discussion.

**Approach: Attend external workshops.** In addition to conducting internal workshops, the CDMRP will continue to attend relevant workshops hosted by other local entities such as the National Institutes of Health (NIH). Attendance at the recent Portfolio Analysis Symposium hosted by the NIH in July 2012 provided a wealth of information to the CDMRP on data analysis tools and approaches that could be applied to peer review processes. The CDMRP remains

committed to communicating and partnering with the NIH and other federal agencies to leverage information and resources.

**Proposed FY2013 process enhancements**

- Implement enhanced training specific to each award mechanism for the Scientific Review Officer, panel chair, and peer reviewers.
- Add a descriptive paragraph, in addition to "strengths" and "weaknesses" for each review criterion in the critique template of the summary statement, to ensure clarity of the critique.
- Provide staff access to the electronic peer review scoring system for real-time monitoring of critique narrative and score alignment.

**Proposed future process enhancements**

- Implement high-definition database searches and software for peer reviewer recruitment (match peer reviewer expertise to each application), and to manage conflicts of interest and potential bias.
- Assess commercial technologies that can provide analyses of the contributions and impact of the CDMRP-funded research to advances toward medical solutions and cures, which will allow the CDMRP to gain information on the effectiveness of its review processes.
- By assessing how and to what degree the CDMRP-funded research has contributed Determine the most cost effective but high quality mode of peer review for each award mechanism: online versus teleconference versus onsite.

## SUMMARY

The CDMRP, USAMRMC, manages its research programs using its established and highly recognized management process. The CDMRP's management is structured to re-evaluate its peer review processes as well as the state of the science on an annual basis, and is designed as "a ship that can turn on a dime." Because of this, the CDMRP has implemented process enhancements, and will continue to do so as noted in this report, to effectively and efficiently improve its review processes. Also, the research programs are able to appropriately shift the focus of their award mechanisms to target the most critical needs along the pipeline of translating basic research to the clinic. Overall, through continued process improvements enabling funding of high-gain research efforts in all phases of the translational pipeline, and supporting investigators that possess the passion and creativity to pursue transformative research, the outcomes of the CDMRP-funded research has a high probability to make clinical and translational research advances.

## REFERENCES

1. Strategies for Managing the Breast Cancer Research Program: A Report to the U.S. Army Medical Research and Development Command (1993) Committee to Advise the Department of Defense on Its Fiscal Year 1993 Breast Cancer Program, Institute of Medicine, National Academy Press, Washington, DC.

2. A Review of the Department of Defense's Program for Breast Cancer Research (1997) Committee to Review the Department of Defense's Breast Cancer Research Program, Institute of Medicine, National Academy Press, Washington, DC.

3. Kaime EM, Moore KH, and Goldberg SF. 2010. CDMRP: Fostering Innovation through Peer Review. Technology and Innovation 12:233-240.

4. Rich IM, Andejeski Y, Alciati MH, Crawford Bisceglio I, Breslau ES, McCall L, and Valadez A. 1998. Perspective from the Department of Defense Breast Cancer Research Program, Breast Dis. 10:33-45.

# Appendix A. Investment Strategy & Research Funded by Type of Research

**•Each Investment Strategy guides the allocation of funds to the different research types to best address the needs of the disease, condition or injury.**

**•Research Funded is recommended by each program's advisory board based on the number and quality of applications received, as well as scientific merit, program relevance, relative impact or innovation, portfolio balance or composition, and adherence to the intent of the award mechanism. FY 2012 awards are not finalized.**

**Proposed Investment Strategy**

**solid color = % of award mechanisms proposed**

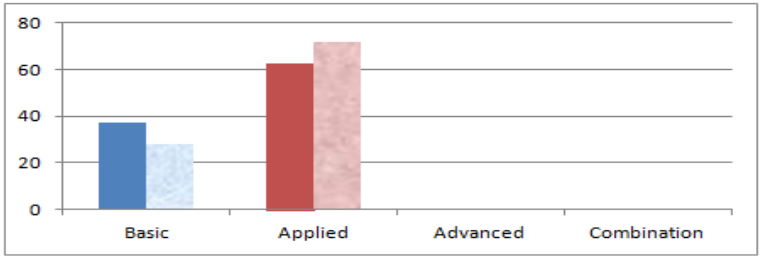
**textured color = % of funding proposed**

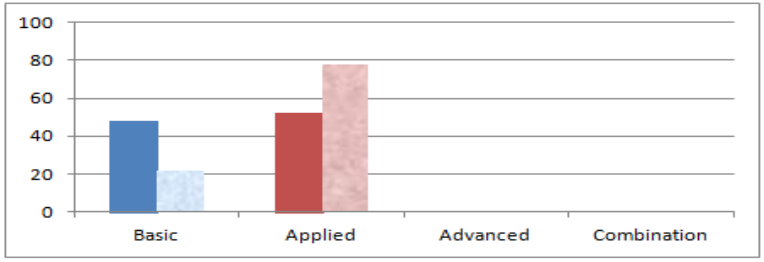
**Actual Research Awards**

**solid color= % of awards**

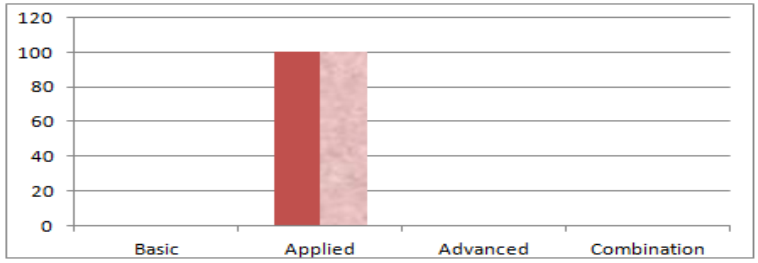
**textured color = % of funding**

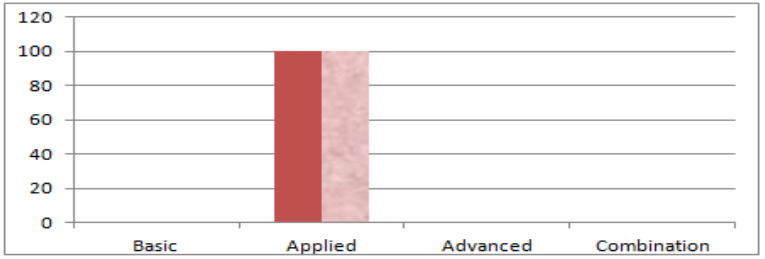
**Amyotrophic Lateral Sclerosis FY09-12**



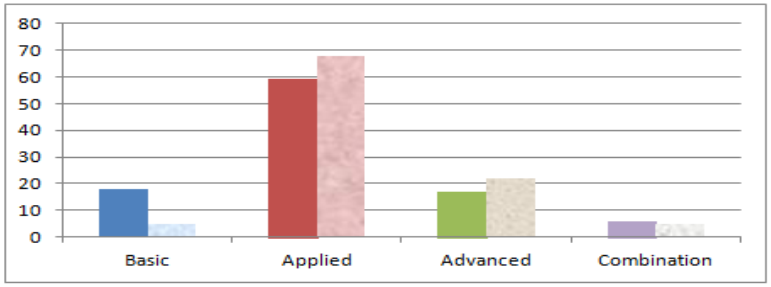



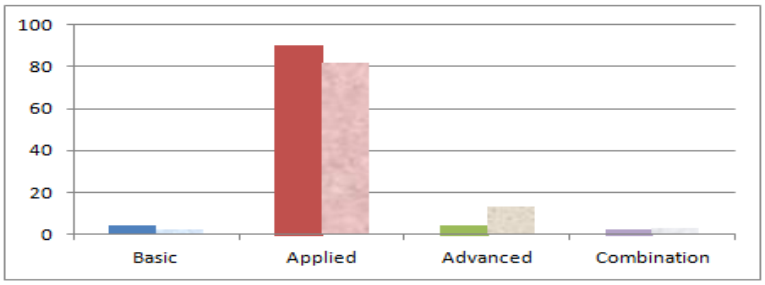

**Army Rapid Innovation Fund FY11**




**Autism Research FY07-12**



## Proposed Investment Strategy

**solid color = % of award mechanisms proposed**

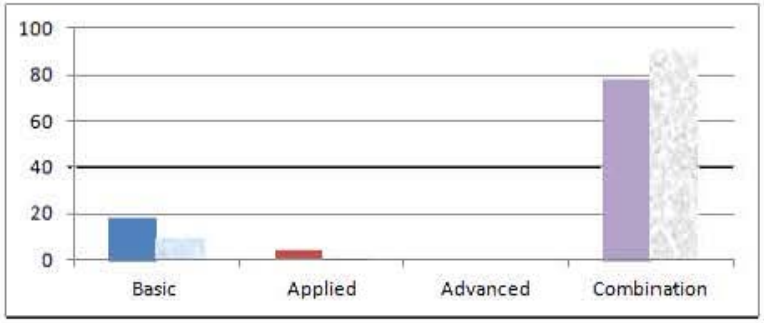
**textured color = % of funding proposed**

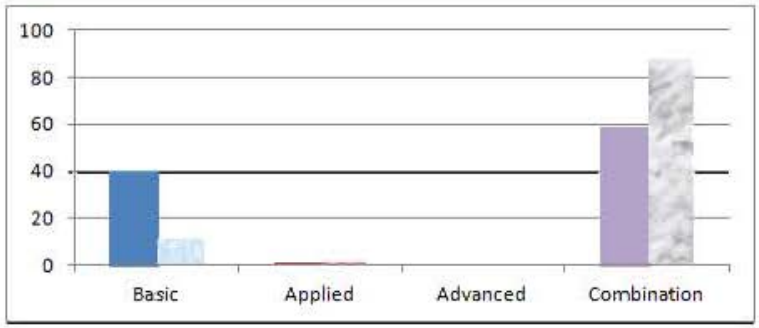
## Actual Research Awards

**solid color= % of awards**

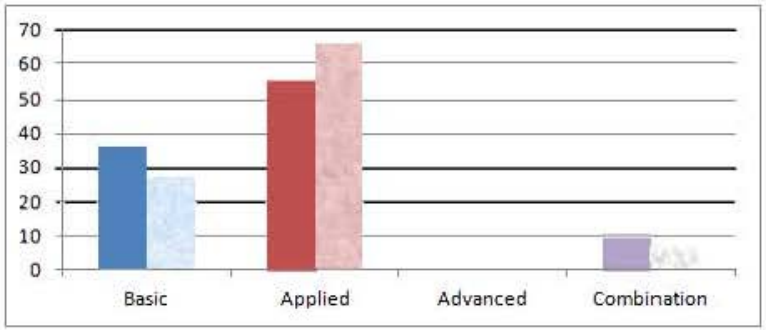
**textured color = % of funding**

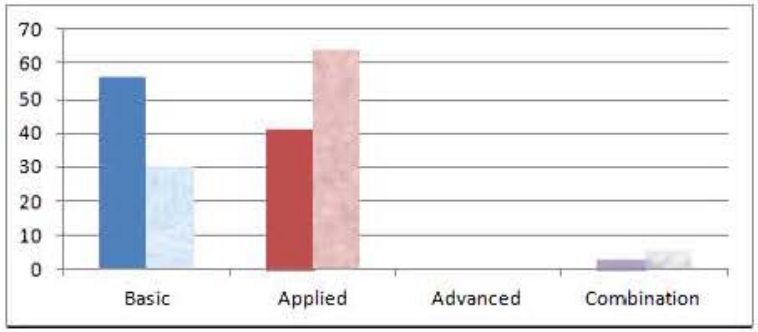
### Breast Cancer FY93-12



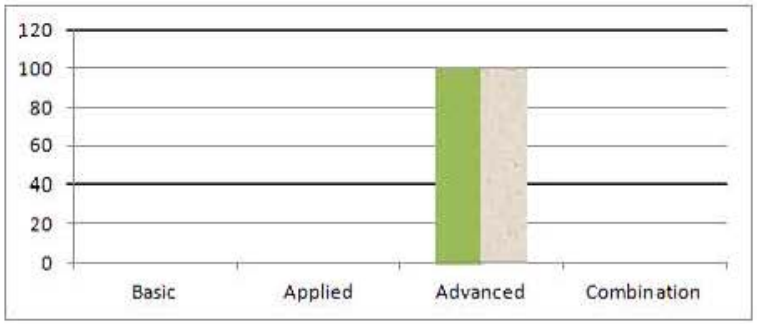



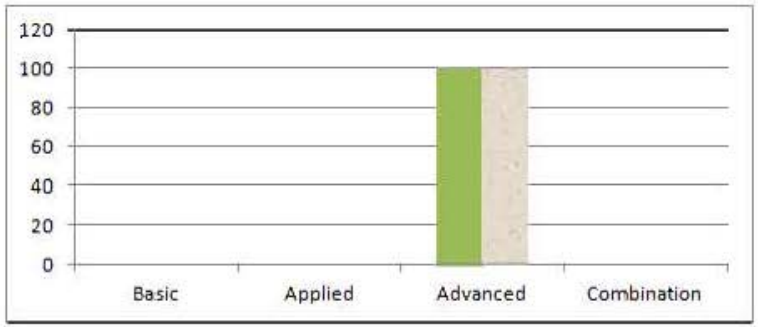

### Bone Marrow Failure FY08-12




### Chiropractic FY10



## Proposed Investment Strategy

**solid color = % of award mechanisms proposed**

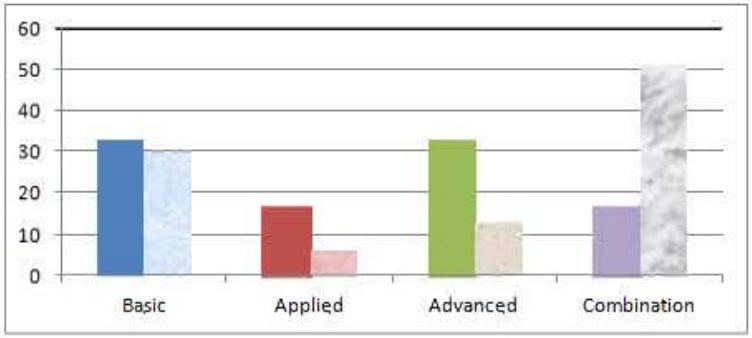
**textured color = % of funding proposed**

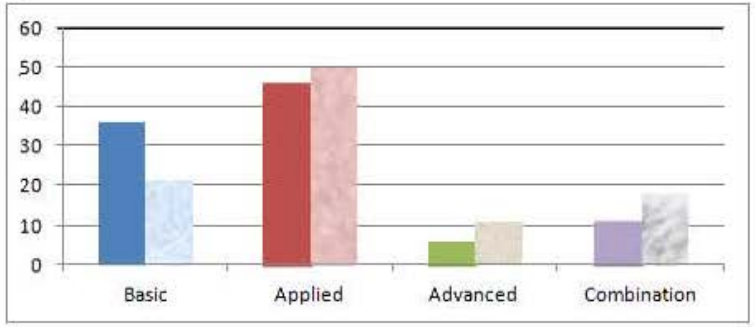
## Actual Research Awards

**solid color= % of awards**

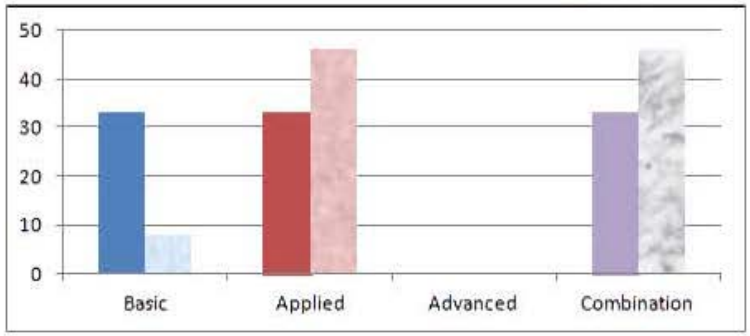
**textured color = % of funding**

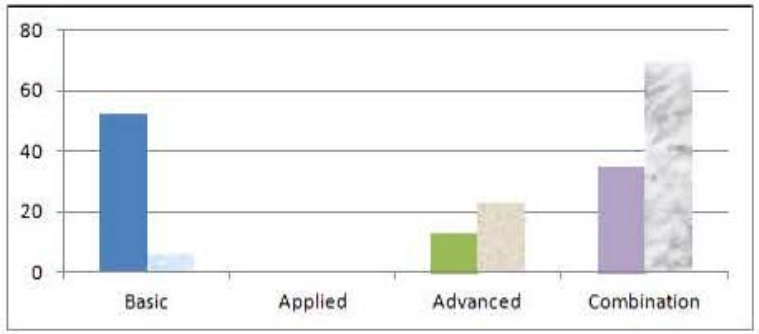
### Defense Medical Research and Development FY09-12



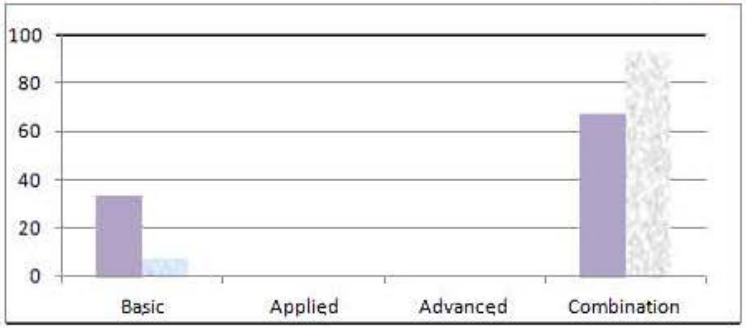



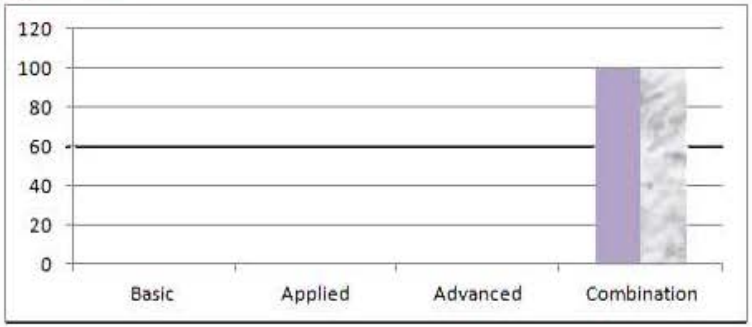

### Deployment Related Medical Rresearch FY08




### Duchenne Muscular Dystrophy FY11-12



## Proposed Investment Strategy

**solid color = % of award mechanisms proposed**

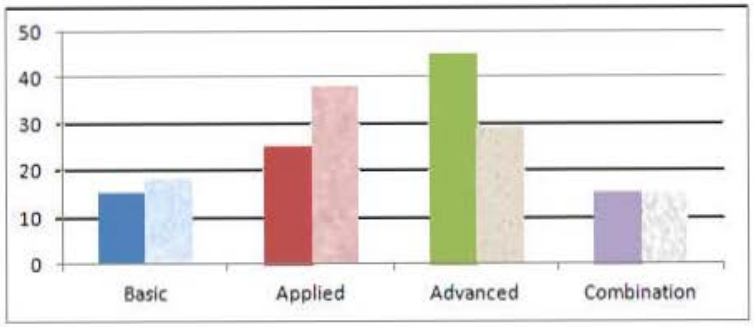
**textured color = % of funding proposed**

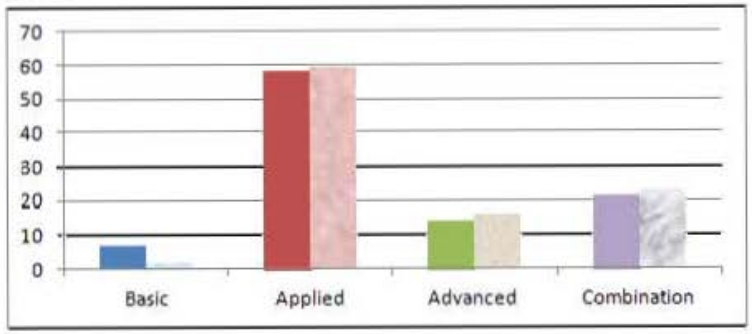
## Actual Research Awards

**solid color= % of awards**

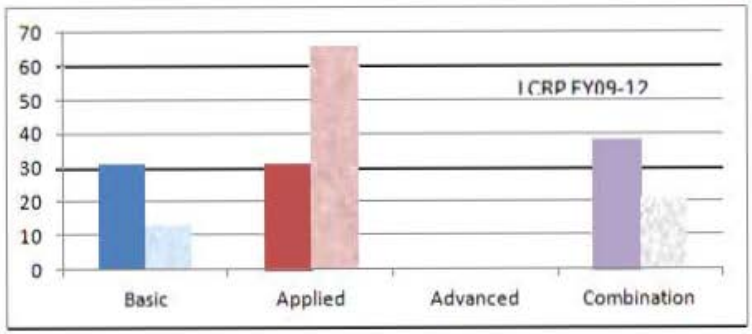
**textured color = % of funding**

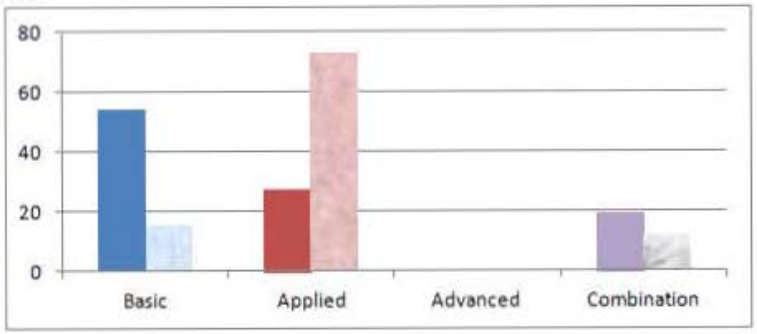
### Gulf War Illness FY07-12



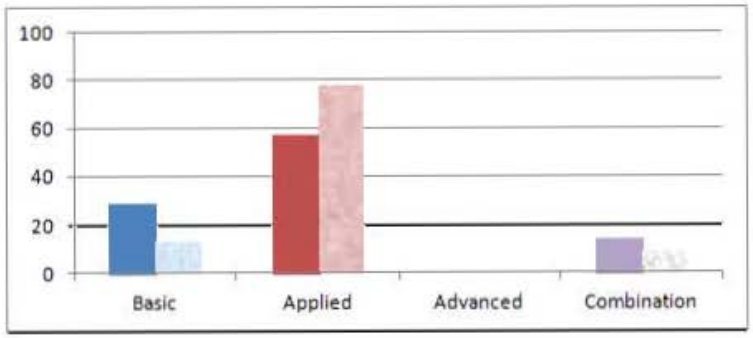



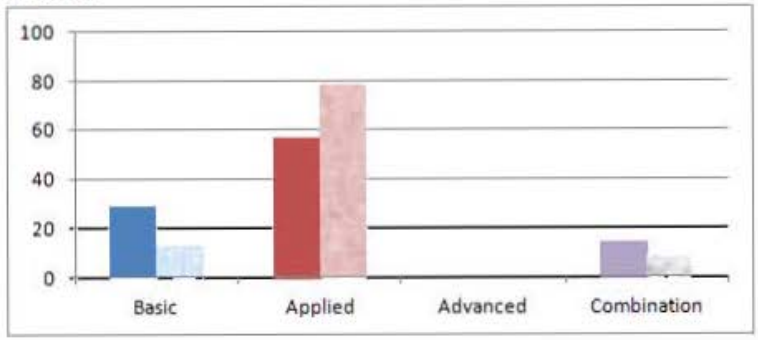

### Lung Cancer FY09-12




### Multiple Sclerosis FY09-12



## Proposed Investment Strategy

**solid color = % of award mechanisms proposed**

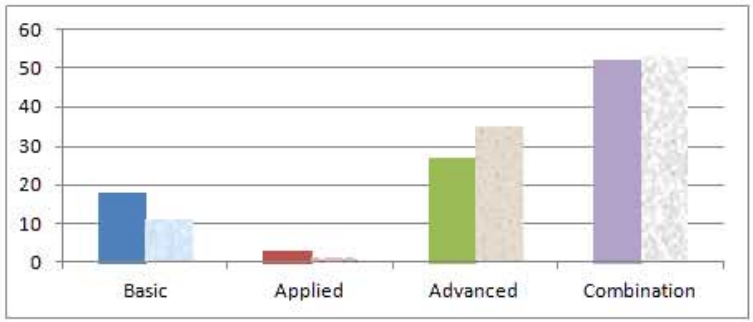
**textured color = % of funding proposed**

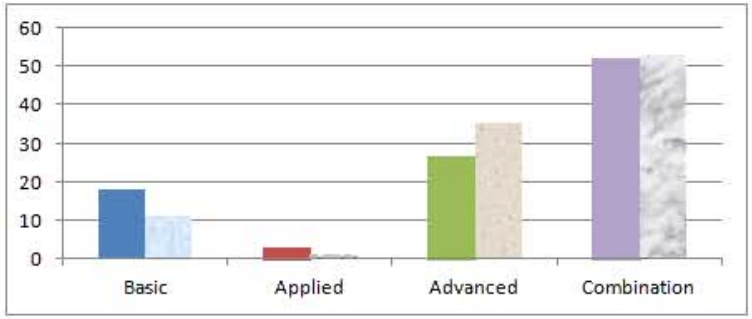
## Actual Research Awards

**solid color= % of awards**

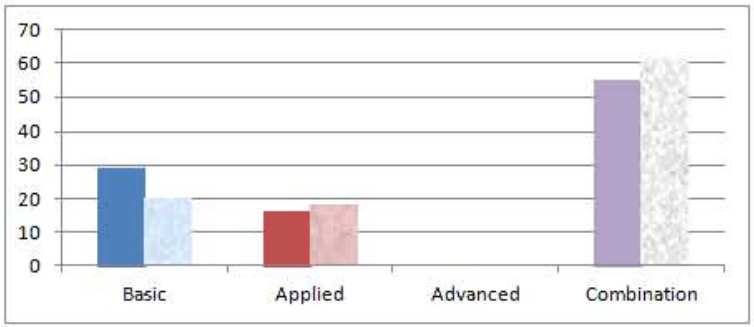
**textured color = % of funding**

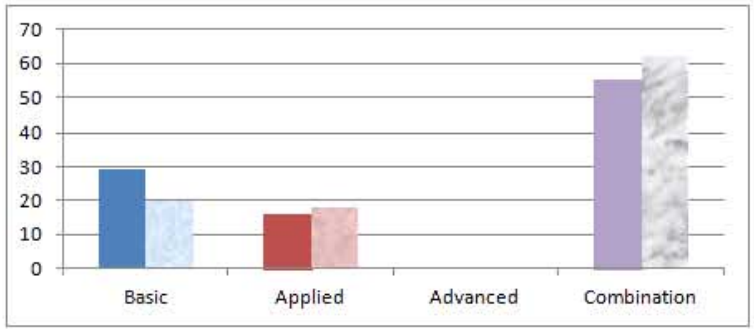
### Neurofibromatosis FY96-12



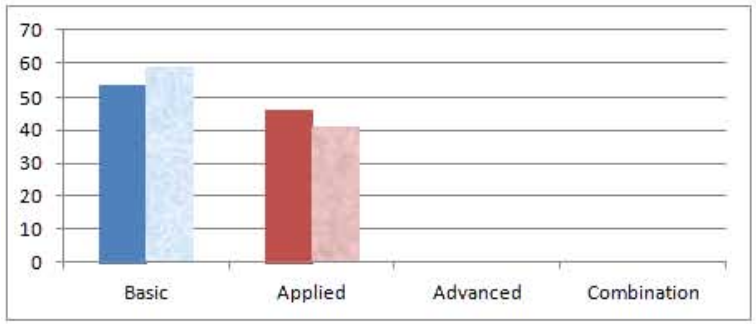



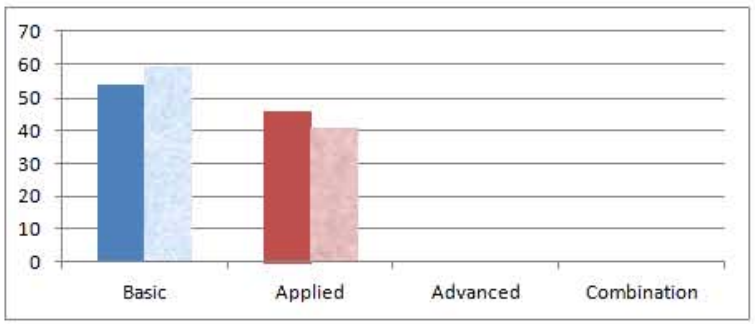

### Ovarian Cancer FY97-12




### Peer Reviewed Cancer FY09-12



## Proposed Investment Strategy

**solid color = % of award mechanisms proposed**

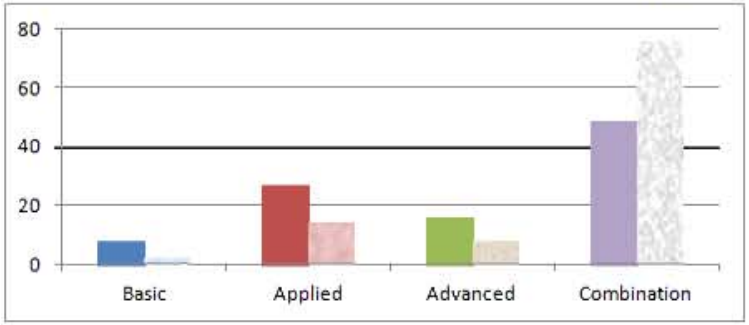
**textured color = % of funding proposed**

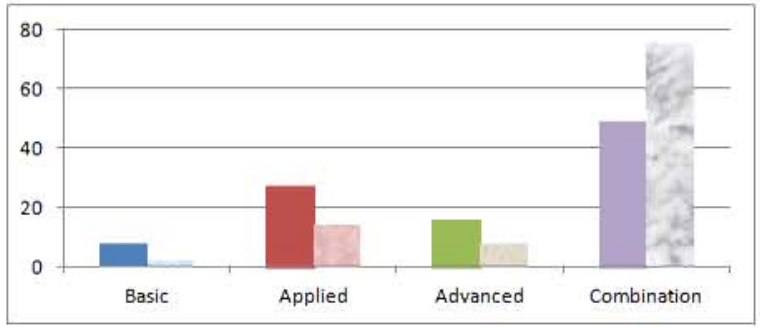
## Actual Research Awards

**solid color= % of awards**

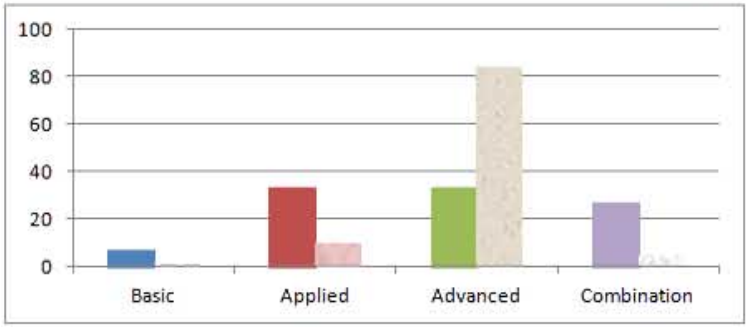
**textured color = % of funding**

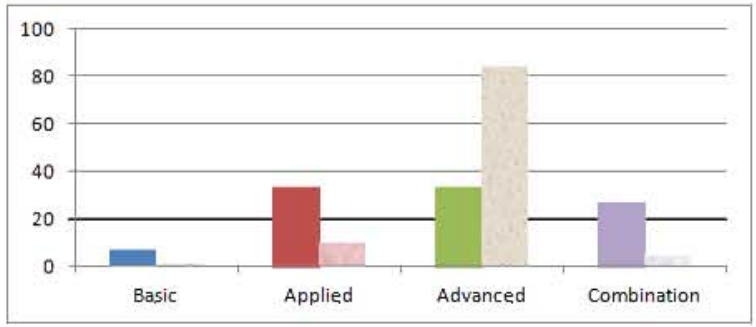
### Peer Reviewed Medical FY99-12



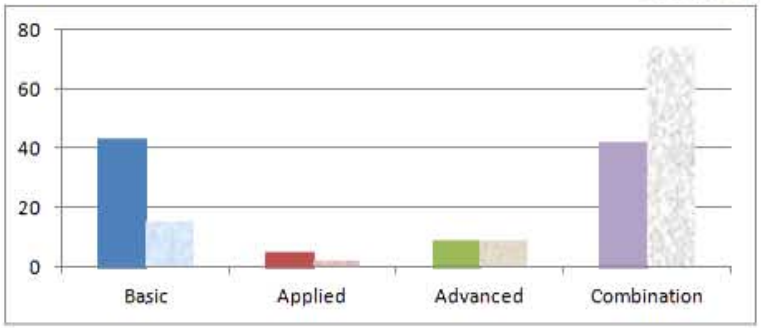



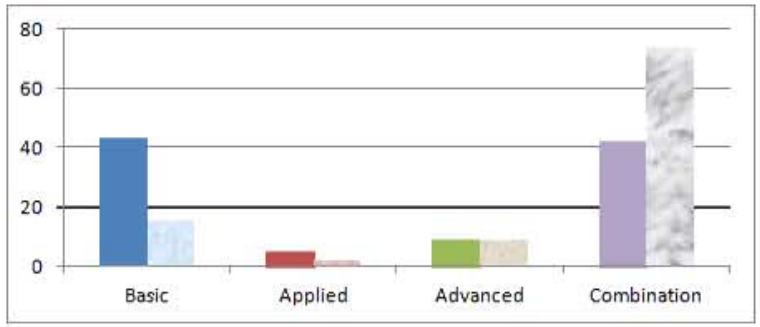

### Peer Reviewed Orthopaedic FY09-12




### Prostate Cancer FY97-12



## Proposed Investment Strategy

**solid color = % of award mechanisms proposed**

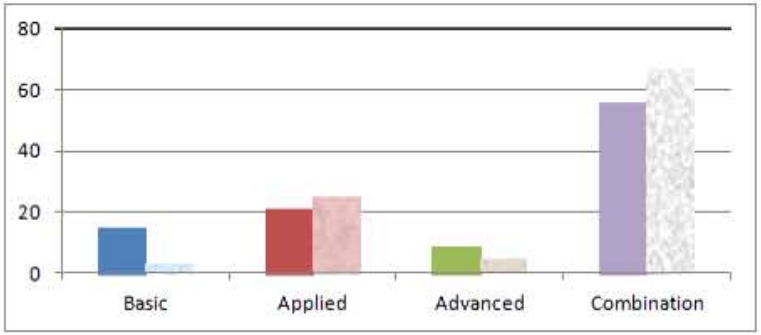
**textured color = % of funding proposed**

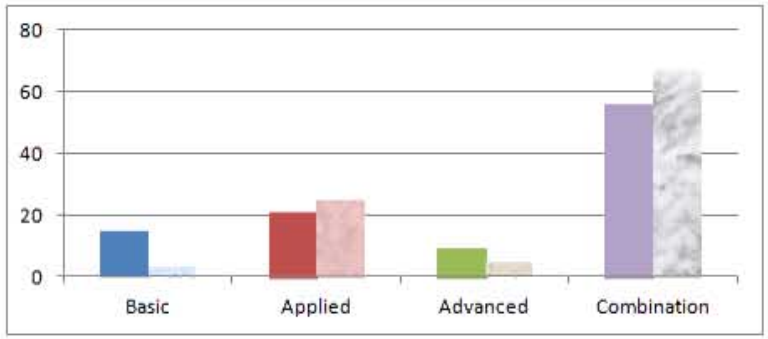
## Actual Research Awards

**solid color= % of awards**

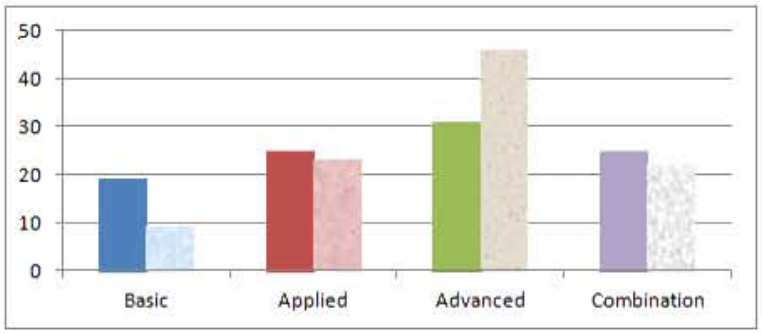
**textured color = % of funding**

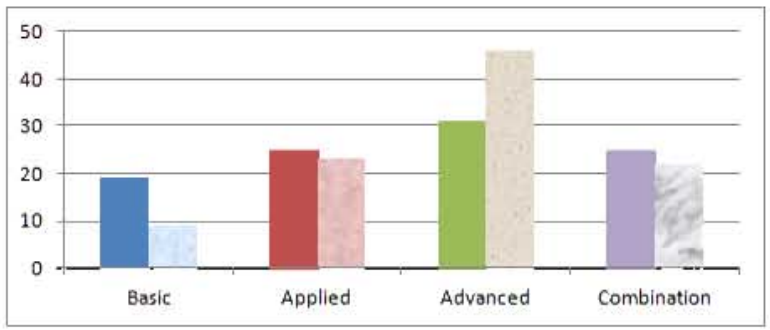
### Psychological Health-Traumatic Brain Injury FY07-12



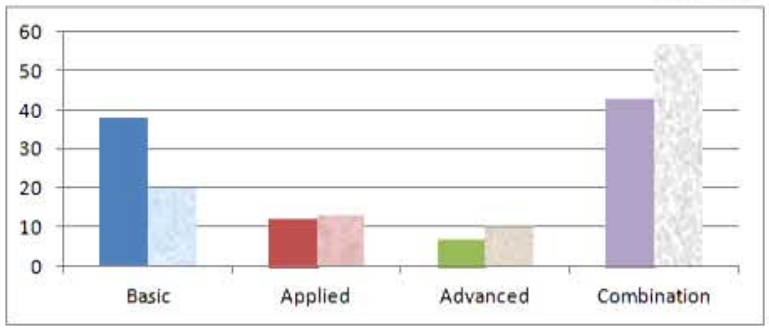



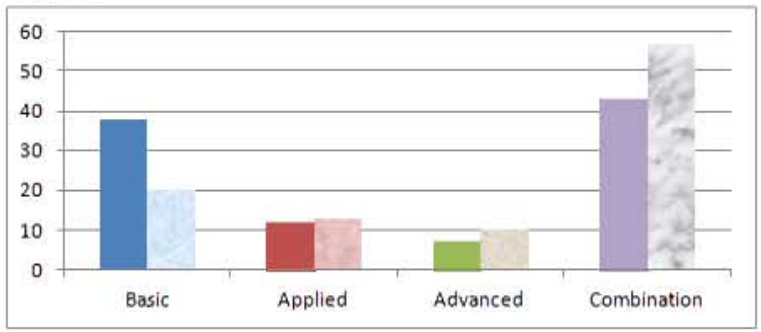

### Spinal Cord Injury FY09-12




### Tuberous Sclerosis Complex FY01-12



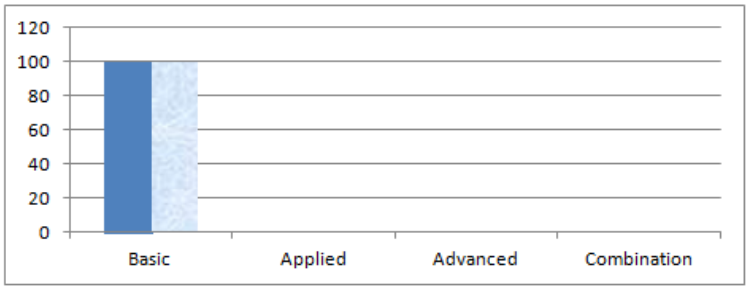



# Appendix B. Research Funded (FY 2009-2011) by Type of Research

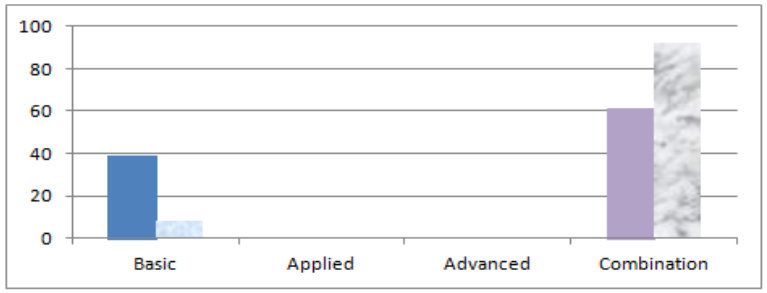
**solid color = % of awards; textured color = % of funding**

**Research Funded is recommended by each program's advisory board based on the number and quality of applications received, as well as scientific merit, program relevance, relative impact or innovation, portfolio balance or composition, and adherence to the intent of the award mechanism.**

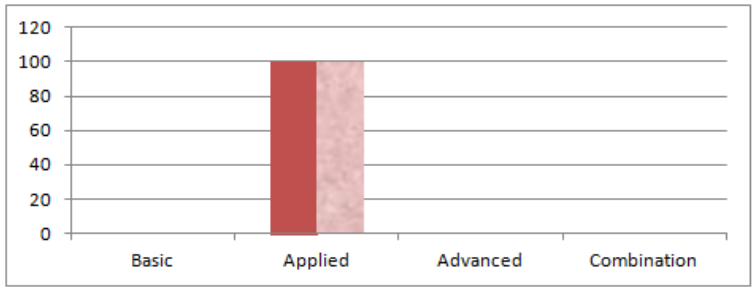
### Amyotrophic Lateral Sclerosis FY09-11



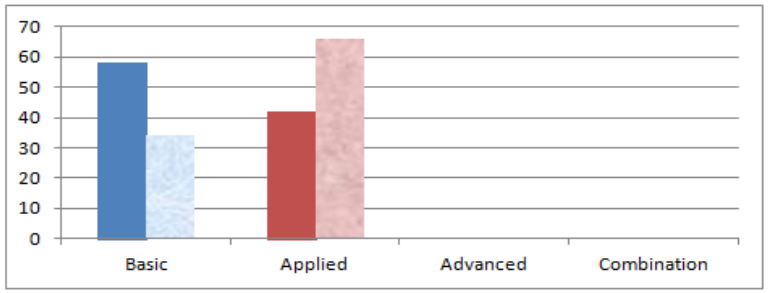

### Breast Cancer FY09-11



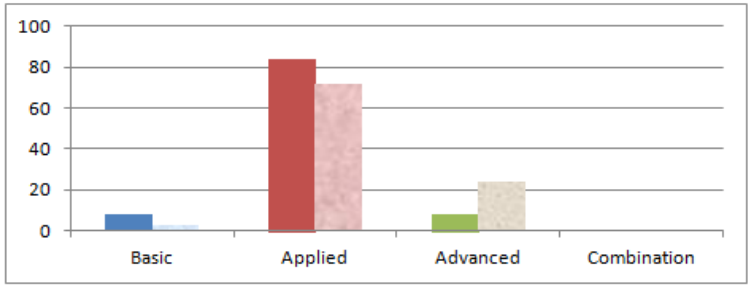

### Army Rapid Innovation Fund FY11



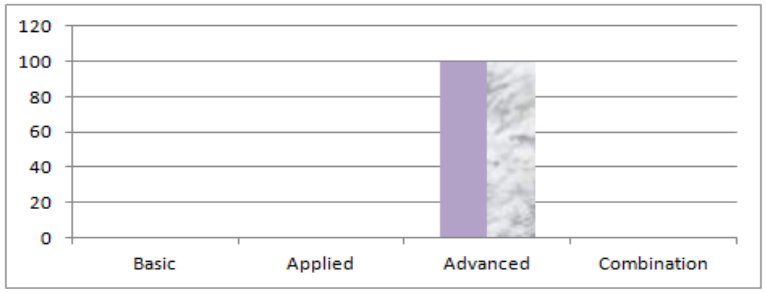

### Bone Marrow Failure FY09-11



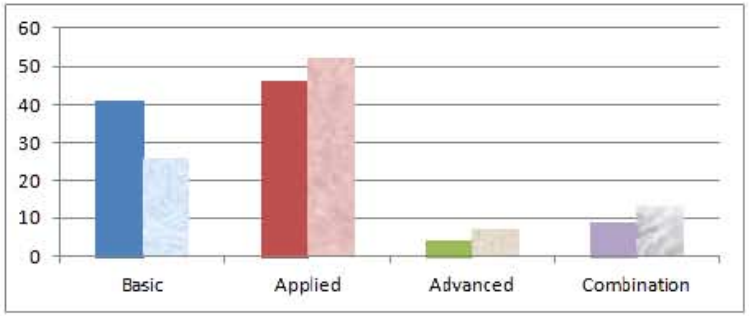

### Autism Research FY09-11



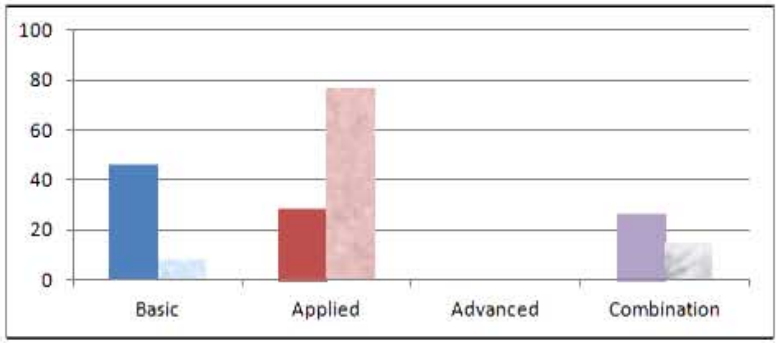

### Chiropractic FY10



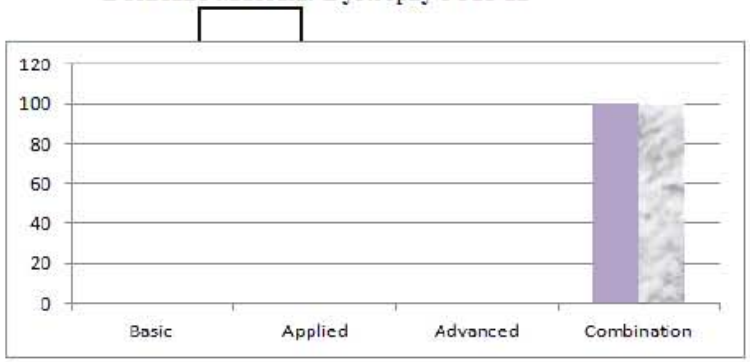
**Defense Medical Research and Development FY09-11**




**Lung Cancer FY09-11**

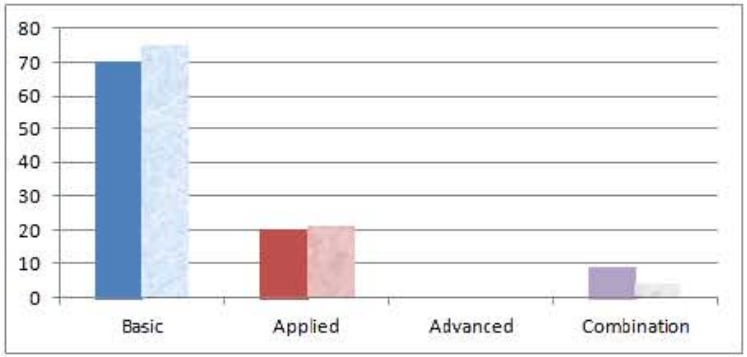



**Duchenne Muscular Dystrophy FY11-12**

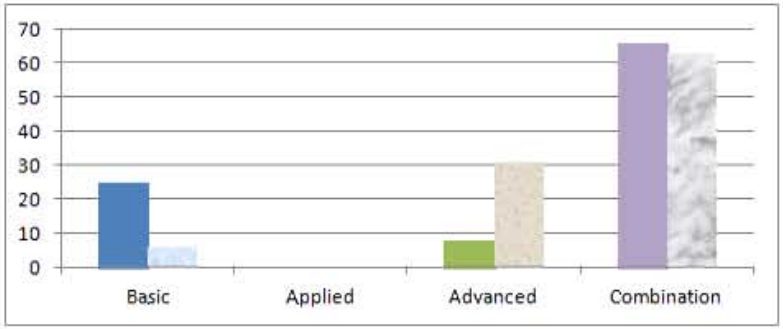



**Multiple Sclerosis FY09-11**

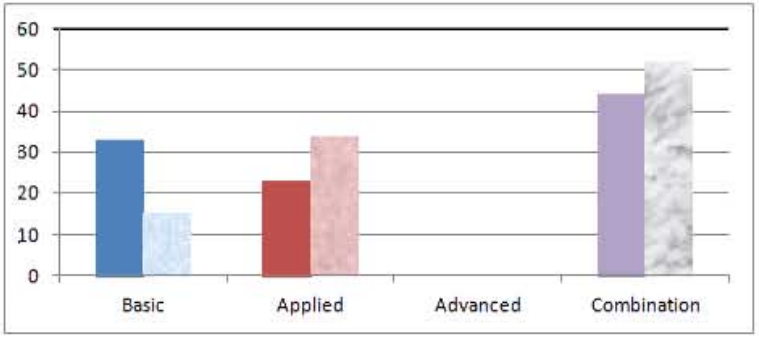

**Gulf War Illness FY09-11**



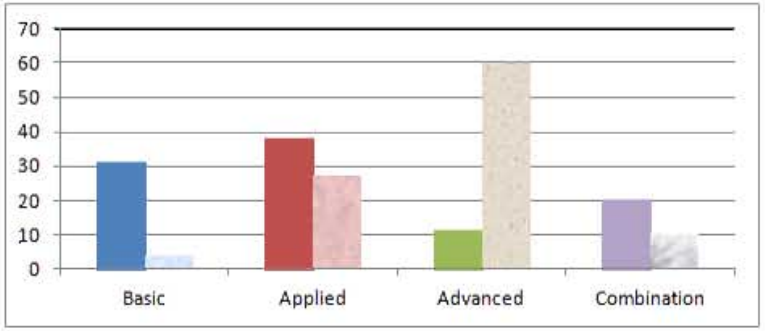

**Neurofibromatosis FY09-11**



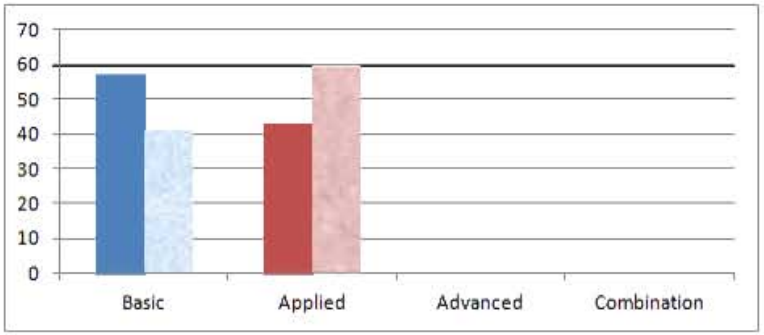
**Ovarian Cancer FY09-11**



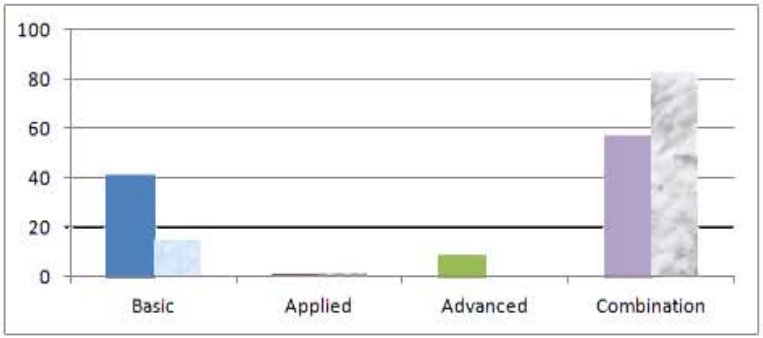

**Peer Reviewed Orthopaedic FY09-11**



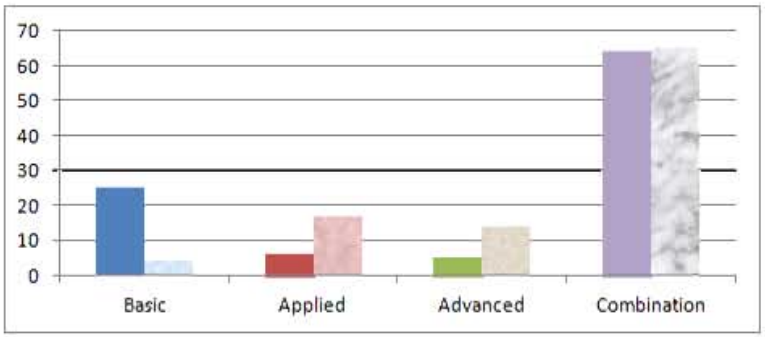

**Peer Reviewed Cancer FY09-11**



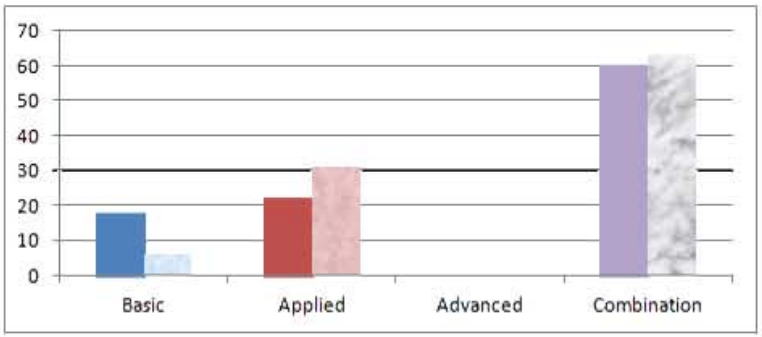

**Prostate Cancer FY09-11**



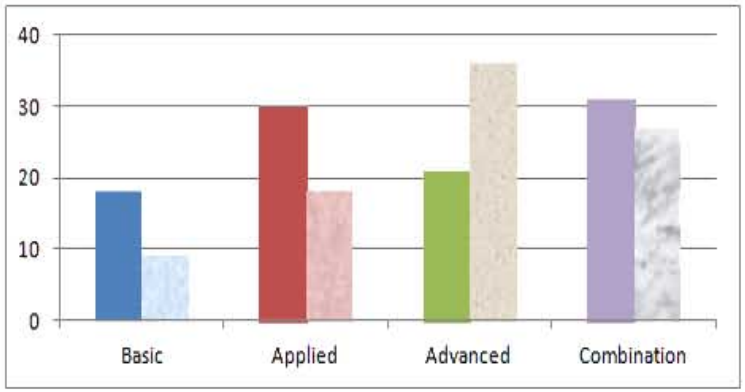

**Peer Reviewed Medical FY09-11**



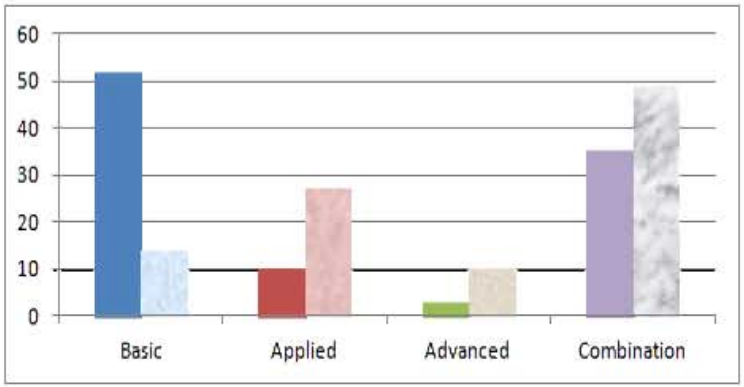

**Psychological Health-Traumatic Brain Injury FY09-11**



**Spinal Cord Injury FY09-11**




**Tuberous Sclerosis Complex FY09-11**



## Appendix C. Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| Clinical Focus: Treatment | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Amyotrophic Lateral Sclerosis** | |
| **2007** - Generated safety and pharmacology data to support an IND filing to test apocynin as a potential therapy for ALS. Apocynin inhibits the production of NOX, a subunit of ROS, thereby reducing microglial cell activation and subsequent degeneration of motor neurons. | **2012** - IND-enabling toxicity and safety pharmacology studies to support phase I clinical trials were conducted successfully and apocynin treatment is now ready for human trials. |
| **2007** - Studied the effect of 39 selected candidates on progressive glutamate toxicity *in vitro* after optimizing dosing of each of these drugs and identified drugs that significantly improve motor neuron survival. The FDA approved and widely used phosphodiesterase 5-inhibitor vardenafil HCl stood out as a lead candidate drug for further *in vitro* and *in vivo* testing. | **2012** - Successfully performed *in vivo* pharmacodynamic studies of vardenafil HCL and confirmed BBB permeability. Plans to initiate connections for testing Vardenafil HCl in a patient cohort are ongoing. |
| **Autism** | |
| **2009** -Initiatied a single site prospective cohort, open label dose finding study of intranasal oxytocin (IN OXT) for the Treatment of Children and Adolescents with Autism Spectrum Disorders. | **2012** - Preliminary evidence suggests that IN OXT is very well tolerated and preparation for a second phase of this study, which involves a multi-site, randomized placebo controlled trial, has been intiated. |
| **2010** - Proposed use of the latest web-based instructional technologies (e.g. web-cams) to greatly increase the availability of the Early Intensive Behavioral Interventions (EIBI) for military-dependent children with Autism Spectrum Disorders (ASD). | **2012** - Remote paraprofessionals are being trained to deliver EIBI for families without direct access to extensive care for ASD. Patient recruitment is currently ongoing. Outcomes may enable professionals in one place to treat children with autism anywhere in the world. |
| **Bone Marrow Failure** | |
| **2009** - Collected primary MDS bone marrow samples, separated them into highly selected populations of stem and progenitor cells , and used a high throuput array based assay to study genome wide patterns. This work contributed to a MDS gene expression repository. | **2012** - Using clinical data associated with the samples in their repository, Dr. Verma went on to determine that TGF-B activation occurred most significantly in low risk subtypes of MDS. These studies are now leading to a clinical trial of LY-2157299 (a novel clinically relevant TGF-B receptor I kinase inhibitor) in low risk subtypes of MDS in collaboration with Eli Lilly. Dr. Verma is the receipient of an FY11 BMFRP Resource Development award to create a large MDS GE expression database to include all subtypes. |
| **Breast Cancer** | |
| **1993** - Preliminary in vitro and in vivo studies to test the efficacy of Herceptin (trastuzumab), a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) receptor. | **2010** - Herceptin is now part of standard-of-care treatment regimes for HER2+ early stage and metastatic breast cancers. |
| **2000** - Clinical trials to assess the efficacy of accelerated, hypofractionated partial or whole-breast radiation therapy designed to minimize the length of radiotherapy required after partial mastectomy. | **2012** - Clinical trial results showed that breast radiation therapy in the prone, rather than the supine, position greatly reduces unnecessary exposure to the heart and lungs, making prone radiotherapy a potential standard choice in breast radiotherapy. Prone radiotherapy is poised to become a standard choice in breast radiotherapy, with industry already adopting modifications of standard radiotherapy tables. |
| **1999** - Preclinical studies on armed activated T cells, which induces the development of "memory" antigen specific cytotoxic T lymphocytes directed at Her2. | **2012** - Led to a Phase I clinical trial in women with Her2+ metastatic breast cancer, which indicated that the treatment infusions are safe and induced long-term anti-tumor responses. The Her2 Bi-armed activated T cells are currently in Phase II clinical trials for treating women with stage II or III breast cancer and women with metastatic breast cancer. |

**Appendix C (*cont*).** Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| **Clinical Focus: Treatment *(cont.)*** | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Breast Cancer** | |
| **1999** - Preclinical studies to develop and test an engineered bispecific single chain Fv antibody capable of simultaneously engaging both HER2 and HER3. This novel agent was designed to enhance therapeutic effects on breast cancers that express both HER2 and HER3 and block the potent pro-growth signaling that occurs when these tumor-associated antigens engage each other upon ligand binding. | **2012** - Resulting technology and parent antibodies were licensed by Merrimack Pharmaceuticals, which developed the agents and concepts into a drug called MM-111, which is currently in early phase clinical trials for treating patients with Her2+ advanced breast cancer. |
| **2002** - Preclinical studies that identified and characterized lead inhibitors of IDO that have pharmacological properties suitable for testing in clinical trials. | **2012** - As a result of this work, Dr. Prendergast demonstrated that the D isomer of an IDO inhibitor called 1MT (D-1MT) has superior anti-tumor properties, and his group discovered IDO2, an IDO-related gene, as one of its important molecular targets. D-1MT is now entering Phase II clinical trials for breast cancer and other cancers, alone or in combination with other drugs, having shown some provocative responses in Phase I/IB trials now completed. |
| **1996** - Characterization of cytotoxic lymphocyte-recognized epitopes on HER2-overexpressing breast tumors, during which E75 (an immunodominant HER2 peptide) was discovered. | **2012** - The E75 peptide has since been developed into an immunogenic peptide-based vaccine under the commercial name NeuVax™ which is now in Phase III clinical trials as a potential breast cancer treatment. |
| **1993** - Initiation of the Phase III clincal trial ATLAS (Adjuvant Tamoxifen Longer Against Shorter), the largest breast cancer treatment trial ever undertaken. | **2012** - Analysis of the ATLAS clinical trial indicated that the rate of breast cancer recurrence or death was lower in women treated with tamoxifen for 10 years versus 5 years; currently in the follow-up phase until 2015. |
| **Defense Medical Research and Development** | |
| **2010** - Developing novel histological techniques to determine the rate of Heterotopic Ossification growth using markers such as osteoblast/osteoclast indices and mineral apposition rate (MAR) to improve surgical planning. | **2012** - Demonstration of the ability to flurochrome label ectopic bone for improved wounded warrior care. This is the first group to demonstrate this potential and makes this team the first to determine quantitative data about the speed of ectopic bone growth. |
| **Deployment Related Medical** | |
| **2008** - Pre-clinical work in animals looking at low-level light therapy for TBI. | **2012** - A pilot study looking at low-light therpy for TBI currently recommended for funding through a USAMRMC Broad Agency Annoucement (BAA) will be initated in humans. The BAA data will be used to support a Phase III clinical trial. |
| **2008**- Development and verification of a treatment system for whole blood which will inactivate pathogens, including viruses, bacteria, donor white blood cells and parasites. The prototype system is designed to be suitable for use in a combat casualty care setting. | **2012**- Development of the device is on track for the next feasibility clinical trial. The IMPROVE II IDE was submitted in February 2012, and approved in March 2012. Communication with the FDA continues regarding pre-clinical test results and future requirements for the device. |
| **Gulf War Illness** | |
| **2006** - Hypothesized that mitochondrial dysfunction contributed to symptoms of Gulf War Illness and sought to assess if coezymen Q10, the primary endogenous lipophilic antioxidant and an electron carrier in the mitochondrial electron transport chain, conferred benefit to overall health and symptoms in GWI. In a 3-month randomized, double-blind trial, 100mg of Coenzyme Q10 was administered twice a day to Gulf War veterans. | **2011** - Significant improvements were reported for pain following exertion providing important preliminary information on effect size and variance that enable a larger trial of coQ10. Increased exercise tolerance has been linked to a range of better outcomes (e.g. to mood, function, cancer, cardiovascular outcomes, cognitive benefits) and mortality benefits – and quality of life benefits previously reported in affected Gulf War veterans. |

**Appendix C (*cont*).** Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| **Clinical Focus: Treatment *(cont.)*** | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Lung Cancer** | |
| **2009** - Discovered that dasatinib, a drug currently used for leukemia, can inhibit the proliferation of DDR2-mutated squamous cell lines both in vitro and in vivo, suggesting that DDR2 may be the first therapeutic target in lung Squamous-cell carcinoma with existing clinically approved drugs. | **2012** - Opened a clinical trial of dasatinib in lung Squamous cell carcinoma at the Dana-Farber Cancer Institute, which recently expanded to a nation-wide study and is recruiting patients at this time. |
| **Neurofibromatosis** | |
| **2005**- Early mechanistic studies investigating the role of the NF1 protein (neurofibromin) in regulation of mTOR pathway activation and subsequently cell growth in astrocytes, Nf1 mouse models & tumor cell lines derived from NF1 patients. | **2012** - These investigations made original and significant contributions to a better understanding of the role of the mTOR pathway in mediating cell growth. This study and other early investigations of the mTOR pathway supported the current testing of Lovastatin and Rapamycin in clinical trials of Neurofibromatosis Type I (NF1). |
| **Peer-Reviewed Medical** | |
| **2002** - Developed CareGuide, a portable sensor system that noninvasively measures muscle pH, muscle oxygen, and hematocrit from light reflected on the forearm to assess tissue perfusion and guide treatment during resuscitation care. | **2012** - FDA approval received in July 2012 for CareGuide™ Oximeter as an adjunct, non-invasive monitor of hemoglobin oxygen saturation of mircrovascular blood in skeletal muscle tissue as the first FDA-cleared device to continuously monitor muscle oxygen saturation and the first device to assess tissue perfusion on patients with pigmented skin. |
| **2006** - Tested novel nociceptin receptor agonists in primates and determined that they produced pain-mitigating effects similar to other clinically used opiates, and demonstrated significantly less severe withdrawal symptoms after chronic use than those observed with morphine. | **2012** - Recently recommended for additional funding through the Joint Warfighter Medical Research Program to generate preclinical efficacy data to support an IND application to the FDA. |
| **Prostate Cancer** | |
| **1997** - Developed and conducted a phase I clinical trial for the proteasome inhibitor PS-341 in inducing apoptosis in androgen-independent prostate cancer. | **2008** - PS-341, now known as Velcade (bortezomib), is the standard of care for multiple myeloma and mantle cell lymphoma. |
| **2002** - Demonstrated the ability of a foreign protein (xenoantigen) to elicit an antigen-specific immune response using nucleic acid vaccines and prostatic acid phosphatase (PAP) as a model anitgen in a rodent model. | **2012** - The agent that was developed from the 2002 findings is now in Phase II clinical trials for the treatment and potentially prevention of prostate cancer. |
| **1999** - Established that the plant toxin thapsigargin can be synthesized into an inactive "prodrug" that could be activated by prostate specific antigen (PCA) expressed on prostate cancer cells, for prostate cancer-specific cell killing. | **2012** - The prodrug is now in Phase II clinical testing for the treatment of prostate cancer. |
| **1999** - Demonstrated the potential of tumor-restrictive gene therapy for metastatic prostate cancer. Specifically, showed that adenovirus could be successfully targeted to metastatic prostate cancer in bone and would replicate to kill the prostate cancer cells only upon androgen-dependent activation of the osteocalcin promoter. | **2012** - The drug (Ad-OC-TK) plus valacyclovir showed no serious adverse events and delayed PSA progression in a Phsae I/II clinical trial. |
| **Psychological Health and Traumatic Brain Injury** | |
| **2007** - Intiated animal studies including pharmacokinetic/toxicokinetic (PK/TK) studies on daily dosing of COG1410. In general, COG1410 is well tolerated and safe at levels where anti-inflammatory and neuroprotective activities in Tramatic Brain Injury (TBI) were observed. | **2012** - Created and filed an Investigational New Drug (IND) application with the FDA to support the Phase 1 human clinical trials testing of COG1410 for victims of TBI. |

**Appendix C (*cont*).** Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| **Clinical Focus: Treatment *(cont.)*** | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Spinal Cord Injury** | |
| **2009** - Tested a novel neuroprotective treatment in rats using an anti-inflammatory antibody (anti-CD11d) aimed at improving outcomes after spinal cord injury. | **2012** - To move the anti-CD11d antibody therapy into a clinical trial for human spinal cord injury, the investigators have entered into an agreement with Eli Lilly who is developing a humanized version of the mouse anti-rat CD11d antibody. |
| **2009** - Demonstration that high Schwann cell concentrations are effective therapeutically after spinal cord injury and improves functional recovery. | **2012** - Created and filed an Investigational New Drug (IND) application with the FDA for use of Schwann cells and received approval to begin a Phase I study. |
| **Tuberous Sclerosis Complex** | |
| **2006** - Biochemical and structural studies investigating how impairment of TSC1/2 function results in the activation of the mTOR signaling network. | **2008** - Published a paper in *Science* describing mTORC1 signaling mechanisms which set the stage for the rational development of drugs targeting the mTOR pathway in TSC. This early research rapidly led to the development of animal models and subsequnetly clinical trials resulting in the first drug approved by the FDA specifically for treatment of individuals with TSC. |
| | |
| **Clinical Focus: Prevention** | |
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Neurofibromatosis** | |
| **2000** - Showed that FDA-approved Gleevec could block the ability of NF1+/- mast cells to stimulate fibroblast proliferation, suggesting that it might work to prevent neurofibromas. | **2008** - Results allowed for fast track approval for a phase 2 trial of Gleevec in children and adults with NF1. |
| **Peer-Reviewed Cancer** | |
| **2009** - Study of the linkage between reactive oxygen species (ROS), genetic and epigenetic changes, and UV radiation leading to melanoma development. | **2012** - The study found a “photochemistry in the dark” phenomena, which is that DNA damage by UV light continued after sun exposure. The delayed sunlight damage could be prevented by an identified agent. This finding could lead to a new formulation of sunscreen to protect the delayed skin damage by sun exposure. |
| **Peer-Reviewed Medical** | |
| **2005** - Conducted the Prevention of Low Back Pain in the Military (POLM) trial to determine if a combined prevention program is more effective at limiting the development of chronic low back pain when compared to the effects of individual evidence-based prevention programs, or a traditional exercise program. | **2012** - Core stabilization has been advocated as a preventative, but this study showed it offered no benefit for decreasing low back pain (LBP). Instead, receiving psychosocial education that reduced the fear and threat of LBP did decrease incidence. This early investigative trial suggests future trials should put more emphasis on translation of the psychosocial education program. |
| **1999** - Sleep Watch: The U.S. Army Sleep Management System. Study created a wrist-watch device that measures movement while awake and asleep to predict cognitive performance capability of soliders in field; multiple patents received. | **2004** - Sleep Watch was patented and has become the "core of the US Army's developing Sleep Management System, a tool to enable commanders to effectively manage sleep to sustain performance in the operational environment." |
| **Prostate Cancer** | |
| **2005** - Study investigated the technical development and early clinical testing of an advanced customized prostate exam for use in a doctors office. The exam involved a magnetic resonance imaging (MRI) guided prostate biopsy in a horizontal bore scanner using a dedicated interventional table. | **2009** - This study provided clinical demonstration of feasibility, tolerance, target stability, and targeting accuracy of the customized prostate exam and the interventional table. This group teamed with Sentinelle Medical Inc. to futher develop this practice and commercialize the table. |

**Appendix C (*cont*).** Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| **Clinical Focus: Prevention *(cont.)*** | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Prostate Cancer** | |
| **2002** - Demonstrated that blocking RANKL can diminish progress of prostate cancer in bone. | **2011** - FDA approval of Denosumab [XGEVA©] for prevention of skeletal-related events in patients with bone metastasis from solid tumors; human monoclonal antibody developed by Amgen. |
| | |
| **Clincial Focus: Risk and early detection** | |
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Autism** | |
| **2007** - Designed assays to investigate newborn blood samples for potential immune biomarkers of autism. | **2012** - In archived newborn dried blood spots, higher levels of neonatal IgM appeared to be a risk factor and maternal IgG antibodies against both of the pneumococcal polysaccharide antigens tested (PnPS14 and PnPS18) appear to be associated with a slight reduction in the risk for autism spectrum disorder. A manuscript describing these results is expected to receive clearance at CDC. The results from the control population in this data set represent the largest database of neonatal IgM levels measured by current state-of-the-art technology and provide invaluable data for clinical reference ranges. |
| **Breast Cancer** | |
| Established a high-risk breast cancer registry to gather genetic and environmental risk infomration about women with familial breast cancer. | **2000** - This registry evolved into the Margaret Dyson Family Risk Assessment Program which serves Philadelphia and its surrounding communities and provides a range of risk assessment, screening, and preventative services to individuals who have a family history of breast and ovarian cancer. |
| **1999** - Early investigations into the molecular biology of Skp2, an oncogene that is overexpressed in breast tumors. | **2012** - The Skp2 oncogene is now known to correlate with poor prognosis and is part of a prognostic test performed in clinical pathology laboratories. |
| **1993** - Initial investigations leading to the discovery of the BRCA2 617delT mutation, one of three founder BRCA1/2 mutations that occur in Ashkenazi Jews. | **1996** - The BRCA2 617delT mutation was patented by Myriad Genetics and BRACAnalysis™ is now available as part of a commercialized test for gene mutations in this group. |
| **2001** - Developed shRNA libraries targeting over 30,000 genes in the human and mouse genomes to provide rapid screening tests to uncover gene regulation and to identify new therapeutic targets. | **2006** - Commercialized Expression Arrest™ shRNA libraries which are ready-to-use, rapid RNAi screens for the entire human and mouse genomes. These libraries are a tool to study gene regulation and identify new therapeutic targets in many diseases and conditions, including breast cancer. |
| **1999** - Intiated a multicenter clincial trial I to validate Sentinel Lymph Node Biopsy (SLNB), or removal of only the first few nodes that receive lymph drainage from the breast, compared to convential axillary lymph node dissection (ALND), as an accurate method to predict the presence of disease in auxillary lymph nodes. | **2010** - Results from a phase III randomised trial indicated SLNB showed no difference in survival and it was concluded ALND is not necessary for all women. SLNB is now the standard for detecting breast cancer invasion. |
| **2006** - A critical study comparing the Molecular Breast Imaging (MBI) technology to breast MRI was performed. | **2010** - Molecular Breast Imaging (MBI) is currently being used as an imaging technique that has greater detection sensitivity than mammography in women with dense breast tissue and is more cost-effective than magnetic resonance imaging (MRI). FDA-approved MBI units are now commercially available. |
| **1995** - Developed a minimally invasive diagnostic procedure for detecting precancerous cells in fluid from breast ducts. | **2000** - This work led to 2 patents, FDA approval of the catheter, and commercilization of the ductal lavage technique. This technique is now used by clinicans to non-invasively and repeatedly sample the ductal epithelial cells in women at high risk for breast cancer. |

**Appendix C (*cont*).** Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| **Clincial Focus: Risk and early detection *(cont.)*** | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Breast Cancer** | |
| **2000** - Performed risk-association studies that discovered a women's single nucleotide polymorphisms combined with personal history can estimate her risk for breast cancer. | **2008** - OncoVue, the first genetic-based breast cancer risk test, is used by clincians to individualize breast cancer screening and monitoring. OncoVue is now commercially available and offered at over 30 breast care centers in the US. |
| **Multiple Sclerosis** | |
| **2009** - Developed a myeloperoxidase (MPO) targeted MRI agent for detection of early, preclinical, and subclinical multiple sclerosis disease activity. | **2012** - Established that MPO-Gd imaging is highly sensitive as an imaging biomarker to report disease activity prior to symptom onset. These pre-clinical studies set the stage for clinical investigations into MPO imaging as a potential early detection strategy for MS. |
| **Neurofibromatosis** | |
| **2002** - Developed and validated a screening protocol for small alterations and multiexon deletions in the SMARCB1gene to confirm the hypothesis that SMARCB1 is a tumor suppressor for schwannomas in the context of familial schwannomatosis. | **2008** - This work successfully identified alterations in the SMARCB1 gene which positively confirm that it is a tumor suppressor for familial schwannomatosis. This work has been replicated by other groups in England and Italy. |
| **Ovarian Cancer** | |
| **2004** - Developed a proteome resource involving integrated proteomic and bioinformatic analyses to identify putative biomarkers of ovarian cancer . | **2008** - Work resulted in OPHID, web-based database to predict interactions between human proteins, and NAViGaTOR, a companion system for visualizing and analyzing protein-protein interaction networks. Thee tools currently support multi level secure access, which enables collaboration with researchers even before the data is ready to be released into public domain. |
| **2009** - Conducted a study that discovered elevated urinary levels of Bcl-2 in women are associated with risk for ovarian cancer. | **2012** - A device for measuring Bcl-2 in the urine is currently being developed for commerical use. |
| **2006** - Preliminary investigations discovered that the Asn372His genotype of BRCA2 significantly increases the risk of ovarian cancer. | **2012** - Genetic screening for BRCA2 mutation is used to assess women's risk for developing ovarian cancer. |
| **Peer-Reviewed Medical** | |
| **2004** - Showed in a Phase I clinical trial that an orally administered vaccine from bovine milk immunoglobulin (BIgG) is effective against diarrhea upon challenge with Enterotoxigenic Escherichia coli (ETEC), a very common cause of diarrhea in travelers and military. | **2012** - Transferred four BIgG products to ImmuCell Corporation for continued cGMP storage and future use in clincal studies. |
| **Prostate Cancer** | |
| **2005** - Produced drugs that attach to prostate tumors and make them more visible in imaging scans. One in particular ([18F]DCFBC) completed toxicity testing and GMP synthesis and was ready for clinical testing. | **2012** - Clinical studies are currently ongoing to evaluate agent as a PET imaging biomarker of detection and aggressiveness. |
| **2001** - Developed the landmark Prostate Cancer Project (PCaP) to study over 2,000 men in Louisiana and North Carolina focused on understanding and resolving the large disparity in prostate cancer incidence and mortality between Caucasian and African American men. | **2010** - This project created an unprecedented and high-impact resource of epidemiological data and biological specimens that are available for numerous health disparity studies that have already begun to uncover major contributors to disparity, such as genetic and societal differences. Clinical impact is already being made in relation to patient-provider communications, treatment decision-making, helth literacy, and dietary factors. |

**Appendix C (*cont*).** Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| **Clincial Focus: Risk and early detection *(cont.)*** | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Psychological Health and Traumatic Brain Injury** | |
| **2009** - Proposed a high prevalence of chronic pituitary and target-organ hormone abnormalities occurs after blast-related mild traumatic brain injury. Objective of the study is to screen basal horomone concentrations in blood and develop accurate, routine diagnosis of hypopituitarism. | **2012** - 42% of the Veterans sampled with blast mTBI were found to have one or more pituitary hormone abnormalities compared to controls. The Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE), requested the PI to consult on the preparation of a reference card for primary care physicians, a set of training slides, and clinical recommendations to address "Neuroendocrine Dysfunction Screening Post Mild TBI." The materials have been produced and were made public and posted on the DCoE website. |
| **Tuberous Sclerosis Complex** | |
| **2004** - Began development of the Tuberous Sclerosis Complex Natural History Database, an internet-based database to collect comprehensive data on individuals with TSC, for use by clinicians and researchers. | **2005** - The Tuberous Sclerosis Alliance, a US advocacy and support organization, assumed control of the development process and contracted with a computer software designer, Tesuji, Inc. to further develop the database. Launch of the database has been piloted and as of July 2012, 1,155 people with tuberous sclerosis complex are enrolled in the project. Information collected through this project helps TSC researchers better understand how the disease affects individuals and should lead to new avenues of treatment. |
| | |
| **Clincial Focus: Diagnostic** | |
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Amyotrophic Lateral Sclerosis** | |
| **2009** - Examined whether human induced pluripotent stem cell-GRPs (glial restricted precursors) have capacity for engraftment, survival, and neuroprotective qualities following transplantation. This study created numerous iPS cell lines from sporadic ALS, familial ALS, and control patient samples and has successfully differentiated these cells into iPSC-derived glial progenitors. | **2012** - An open-access collection of fibroblast lines from patients carrying mutations linked to neurological disease was created and published. Cell lines from the CDMRP funded studies have been deposited in the National Institute for Neurological Disorders and Stroke (NINDS) Repository at the Coriell Institute for Medical Research and can be requested by any research group for use in in vitro disease modelling. There are currently 71 mutation-defined cell lines available for request from a wide range of neurological disorders and this collection will be continually expanded. This represents a significant resource that will advance the use of patient cells as disease models by the scientific community. |
| **Breast Cancer** | |
| **2003** - Contributed to the original discovery of the PTEN (phosphatase and tensin homolog) gene. PTEN is one of the most frequently mutated genes in several cancers, and PTEN mutations have been shown to be predictive of aggressive cancer. | **1997** - A PTEN test is commercially available to confirm PTEN mutations for clinical and prenatal diagnoses and identification of at-risk family members. |
| **Ovarian Cancer** | |
| **2003** - Initial investigations identified 5 new biomarkers for ovarian cancer with positive identification. Biomarkers were validated in 3000+ samples | **2009** - OVA1, an in vitro diagnostic multivariate index test, is approved by the FDA and is the only approved blood test to help determine if an ovarian mass is malignant or benign prior to surgery, facilitating surgical planning and identifying patients for referral to a gynecologic oncologist. |
| **Peer-Reviewed Medical** | |
| **2005** - Ultrasound and telemedicine technologies were combined to create a method for the reliable and rapid assessment of newborn infants at risk for heart disease at remote healthcare facilities via telediagnosis. | **2009** - The TeleEcho system developed from this project was shown to allow geographically distant cardiology specialists to supervise real time cardiac ultrasounds performed by physicians and nurses trained to operate a small, hand-held ultrasound device. Early clinical testing enabled physicians to make key decisions regarding patient transfer which saved lives and decreased unnecessary transports. Promising results supported further expansion of the system to other medical centers within the doD and could eventally be used by civilian rural healthcare systems. |

**Appendix C (*cont*).** Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| **Clincial Focus: Diagnostic *(cont.)*** | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Psychological Health and Traumatic Brain Injury** | |
| **2007** - Developed a portable, military ready, sensitive and rapid eye tracking diagnostic device for individuals with mild traumatic brain injury (mTBI). | **2012** - USAMRMC market research shows Eye-Trac is the only system that can meet the Government's requirements allowing commanders to quantify cognitive function in Soliders and make informed decisions on Solider mission readiness. As of Dec 2012, there is a sole source purchase document that references this market analysis in the public domain. |
| | |
| **Clincial Focus: Supportive care and Quality of Life** | |
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Autism** | |
| **2010** - Development of a virtual reality simulator and application to evaluate and enhance the driving skills of individuals with Asperger's and high functioning autism. | **2012** - This is the first study to investigate the efficacy of virtual reality training to enhance the complex cognitive-motor-perceptual skills needed for driving in individuals with Autism Spectrum Disorder (ASD). This unique effort could immediately impact the likelihood of independence/self sufficiency for some of the rapidly increasing population of individuals with ASD. |
| **Breast Cancer** | |
| **2002** - Contributed to the intial development of a website, BreastCancerTrials.org, that educates patients about breast cancer clincal trials and matches them with appropriate studies. | **2005** - A regional pilot test of BreastCancerTrials.org was performed in northern California and underwent a national expansion in 2007. |
| **2002** - Created an infrastructure for a population-based mammography registry in NC focusing on a largly rural population. | **2005** - The Carolina Mammography Registry became a member site of the NCI Breast Cancer Surveillance Consortium. This database provides a resource for researchers to study mammography screening on a national level. |
| **Neurofibromatosis** | |
| **2002** - Formed a multi-institutional consortium that developed critical neurofibromatosis mouse models for almost all of the tumors that arise in individuals with NF1 and NF2. | **2009** - Mouse models have been widely distributed to more than 50 laboratories around the world and has contributed to additional advancements in NF research, including the testing of new treatments for the complications of NF1 and NF2. |
| **Peer-Reviewed Medical** | |
| **2004** - Combined a hybrid orthotic brace and muscular stimulation to assist paraplegics in standing and walking, and demonstrated in proof-of-concept trials that the system allowed users to stand, walk, descend stairs, and rest in a static, upright position. | **2011** - First-in-human testing showed prototype device was able to support the user, supporting the patient's weight and delaying fatigue during use, allowing the patient to prolong walking durations and provide improved knee and hip stability. PI has a partnership with commercial company [Parker-Hannifin] that is facilitating further design improvements to reduce weight of the device. This group was recently recommended for additional funding through the Joint Warfighter Medical Research Program to develop the prototype into a self-contained, portable, and independent system suitable for clinical testing outside the laboratory. |
| **Peer-Reviewed Orthopedic** | |
| **2009** - Developed and tested a physical exotendon device that facilitates walking for individuals with significant mobility impairments. | **2012** - The KickstartTM Kinetic Orthosis is now a commercially available product for individuals with weakened muscles or disabilities seeking to regain mobility. This group was recently recommended for additional funding from the Joint Warfighter Medical Research Program to develop an outcomes tracking technology that will enable the investigators to perform a field study to investigate the device's efficacy. |

**Appendix C (*cont*).** Basic and/or applied early-phase clinical research projects by CDMRP-funded investigators that have led to advanced clinical application.

| **Clincial Focus: Supportive care and Quality of Life *(cont.)*** | |
|---|---|
| **Initial Research Stage (Then)** | **Clinical Application (Now)** |
| **Peer-Reviewed Orthopedic** | |
| **2009** - Under an independent award, Dr. Glaister developed a sensory feedback device that can be used to deliver vibrotactile stimulation to the residual leg from the prosthetic foot in response to pressures from the bottom of the foot. | **2012** - This group was recently recommended for additional funding from the Joint Warfighter Medical Research Program to further develop the prototype device into a self-contained unit suitable for clinical use and to perform a clinical trial to determine if the device can accelerate rehabilitation for lower limb amputees. |
| **2010** - Because stress and strain of war add to the prevalence of low back pain, making it one of the largest causes of attrition in Soldiers in combat, this study is investigating early physical therapy access for low back pain using a treatment based classification (TBC) algorithm. The goal is to identify greater improvements in function and quality of life and decreased healthcare utilization over 1 year as compared to a stepped "usual care" strategy. | **2012** - A study was published by MAJ Rhon's primary mentor, Dr. Fritz in the May 2012 issue of Spine. The findings indicate the fiscal benefits and reduction in healthcare costs associated with early physical therapy. The current PRORP-funded study is the first to validate these findings in a military setting. A trial was successfully registered in March 2012. |
| **Psychological Health and Traumatic Brain Injury** | |
| **2009** - Initiated a 12-month randomized controlled trial comparing supported employment plus Cognitive Symptom Management and Rehabilitation Therapy (SE-Cog) to enhanced supported employment (ESE) for OEF/OIF veterans with mild to moderate traumatic brain injury (TBI) who are unemployed and want to return to work. | **2012** - Veterans who received CogSMART were more likely to obtain competitive employment in the course of supported employment (60% vs. 48%). These results suggest that CogSMART, in the context of supported employment, may improve post-concussive symptoms and work outcomes. The CogSMART manual has been finalized and is available via email. It has been distributed to over 110 clinicians, mainly at VA and DoD facilities. |
| **Spinal Cord Injury** | |
| **2010** - Non-human primate study showed promising pre-clinical functional and safety data that multielectrode stimulation array device implanted into the forearm can restore motor grasp hand function. | **2012** - Ongoing research is working to connect this device to a multielectrode stimulation array device implanted into the motor cortex that will drive complex hand movements. |