Heterogeneous Integration Technology Demonstrations For Future Healthcare, IoT, and AI Computing Solutions

J.U. Knickerbocker, R. Budd, B. Dang, Q. Chen, E. Colgan, L.W. Hung, S. Kumar, K. W. Lee, M. Lu, J.W. Nah, R. Narayanan, K. Sakuma, V. Siu, & B. Wen

IBM T. J. Watson Research Center, 1101 Kitchawan Road, Yorktown Heights, New York 10598
Email: knickerj@us.ibm.com, Tel: 914-945-3306

Abstract - **Innovations in healthcare, diagnostics, sensors and data analysis with Artificial Intelligence (AI) learning / recommendations offer opportunities for improved personalized healthcare, lower costs and benefits to the medical industry. The age of personalized human health monitoring has begun. Human health monitoring using fluidic diagnostic monitoring, non-invasive sensors, wearables (electronic health sensors), implanted health sensors, sound, visual images, and combinations of these data trends offer individuals personalized healthcare guidance. The data, analytics and recommendations from these personalized solutions are beginning to aide our early detection and understanding of health risks from chronic diseases and overall health / wellness. Examples include: cardiovascular disease, diabetes, oncology / cancer, kidney disease, elder care, Parkinson / Huntington Diseases, and many other healthcare applications.**

Rapid advancements of innovative healthcare diagnostic tools, health and environmental sensors along with data trending and analysis using AI systems or platforms can provide industry disruptions in healthcare. AI systems already aid health professionals and individuals with knowledge and recommendations that offer the promise of improved quality of life and lower healthcare costs. Examples such as: (1) earlier chronic disease detection and potential for disease progression delay or prevention, (2) understanding individual behavior, medication treatments and effectiveness of the treatments on activities of daily living and (3) personalized care based on your DNA, medical diagnostics and your healthcare trends relative to your healthcare needs and options to manage your quality of life.

In this paper, we describe both new technologies and advancements to heterogeneous integration technology tools, materials and processes that provide differentiating electronics for future healthcare diagnostic tools and sensors. These new technologies are being applied to targeted applications in healthcare diagnostics and sensor monitoring for precision diagnostic data, smaller product size and much lower costs. Data streams can leverage AI to provide smart personalized healthcare guidance or solutions that compliment existing technology and data to partners such as healthcare professionals, patients and clients. In many applications, we leverage industry available technology or benefit from these new technology advancements to provide for the best system solution. Examples of these new and advancing technologies include:

(1) Precision handling thinned wafers with large die, small die, multi-die, sub-components, components and substrates technologies,

(2) Injection molded solder (IMS) technology for wafers (TSV and / or interconnection) and substrates,

(3) Precision micro-component, die, multi-die substrate and multi-component assembly / integration technology for healthcare, IoT and AI Systems,

(4) Precision laser micro-machining, cutting and welding technology,

(5) Flexible multi-channel, micro-fluidic systems for smart sensing, point of care (POC) diagnostics, and AI and

(6) Small form factor micro-systems and energy solutions / technologies that support future healthcare, IoT, and AI linked computing solutions.

Examples of key challenges and advantages of these technologies for the targeted applications are shared relative to current industry standard solutions. Highlights on future demonstrations in progress at the time of writing this paper are targeted for our 2018 ECTC presentation and other future technical publications.

I. INTRODUCTION

Imagine a "better world" where advancements in (1) electronic technology, (2) biology / healthcare, and (3) data / machine learning can provide insights for personalized healthcare and potentially lead to a high quality of life. These insights are advancing our health and wellness today. In time, ongoing deep levels of research through diagnostic tools, modeling and improved disease understanding have the goal to delay or prevent some diseases.

This "better world" has already arrived and begun to help people based on research from around the world. For example, in 2017, R. Garnavi et al. (Australia) have reported medical imaging with specialized retina photography and AI that can help pinpoint tiny pathol\diabetic patients' eyes and reveal signs of diabetic retinopathy (DR), which is one of the worlds leading causes of blindness [1-3]. Recommended screening and treatments following early detection is estimated to avoid blindness for up to 95% of patients who if left untreated, would go blind. In a 2016 (USA) study, oncologist, Dr. N. Sharpless and pathologist, Dr. N. Patel, of the University of North Carolina Lineberger Comprehensive Cancer Center reviewed cancer treatment insights from work with Watson for Genomics [4]. In the review, 1000 cancer patients data and treatment recommendations was 99% aligned with oncologist's / tumor board therapy recommendations. In addition, in nearly 300 patients, Watson also identified clinically actionable information that had not been found by the humans working without Watson's help.

Ongoing deep research, which leverage advancing diagnostics, molecular modeling, machine learning and artificial intelligence, offer great promise for personalized precision medical care. These future advancements offer the opportunity to delay or prevent some diseases. Computational biologist Rapsomaniki (Switzerland) is studying single human cells according to their cell cycles. She says human cells may last days for some cells (Stomach lining) to 30 years (bone cells). To better understand human tumors she is characterizing single cells composition rather than bulk characterization techniques that can mask their variability. Rapsomaniki et al. report [5] single-cell approaches such as mass cytometry combined with computation, called

CellCycleTRACER, which can pinpoint the proteins at a single-cell resolution, within the data for the first time. R. Zhou and J. Weber (USA) with collaborators have advanced molecular modeling to reveal the underlying molecular mechanism that links personal genetic information to the efficacy of cancer immunotherapy [6, 7 & 8]. Together with Columbia University and the Memorial Sloan Kettering researchers (USA), they are bringing understanding to the molecular interactions that allow current immunotherapies to be effective. These cancer immunotherapies harness a person's immune system to target and kill cancer cells. They imagine a future in which cancer treatments are tailor-made for particular cancer subtypes and for each individual patient. Personalized medicines could equip a patient's immune cells with weapons that uniquely identify and destroy mutant cancer cells and leave normal, healthy cells unharmed. Molecular modeling showed individuals with HLA B44 supertype, had a significantly higher chance of survival from the immunotherapy for melanoma and lung cancer. The researchers discovered genes associated with how killer T cells recognize cancer cells are essential for successful immunotherapies. These critical genes produce "human leukocyte antigens" (HLAs), protein molecules that bind to cancer-specific peptides that appear on the cell's surface. The presence of the HLAs allows killer T cells to identify and destroy their cancer cell targets.

Advancing electronics, sensors, diagnostic chips derived from new generations of materials, processes and equipment combined using advanced heterogeneous integration offer precision healthcare tools that will change the world. These new tools, systems and services can provide precision data, high volume, low cost in a mobile platform for use in a hospital, medical clinic, nursing home, drug store, office, home or car. Just as computing has scaled from large refrigerator sized systems to desk top and lap top to hand held smart phones, this new age of sensors and diagnostic tools is scaling from bench top tools to hand held diagnostic tools to wearable's (wrist watch size) and to healthcare sensors, IoT sensors and emerging heterogeneous integrated micro-systems that are smaller than the diameter of one human hair.

Together we are on a journey of change that requires our best efforts across disciplines and understanding including electronics, biology, human DNA / RNA, precision medicine & diagnostics, deep disease understanding and AI. Personalized and secure data profiles, trending and algorithms with advancing machine learning & prediction will continue to aide society for a "better world."

II. Technology Advancements & Demonstration Results

A. *Precision handling materials, processes and tools*

Precision handling thin silicon wafers using glass handle wafers, silicon handle wafers, temporary or permanent adhesives and bonding has been advancing at IBM Research for more than 15 years. These handling technologies have supported processing thin wafers, die, substrates and components for large X-Y size with thin form factors (prior demonstrations) and also for small size and thin form factors (current demonstrations). The small size and thin form factors handling as well as low cost precision integration are becoming more important for mobile, healthcare and high volume IoT applications.

Prior technology publications using temporary bonding adhesives and room temperature laser debonding equipment for glass handle wafers [9] and for silicon handle wafers [10] have been reported in 2014 and 2016, respectively. Prior technology demonstrations with processing of thinned silicon interposers, thinned large die and 3D thinned die stacks have been reported that used handle wafers for successful results [11, 12, 13, 14]. Examples of these 50 μm thickness, large X-Y size Si interposers and 50 μm thickness, large size die from prior demonstrations are shown below in **Figures 1 to 4**. Application examples supported high performance computing systems and high-performance memory stacking technology.

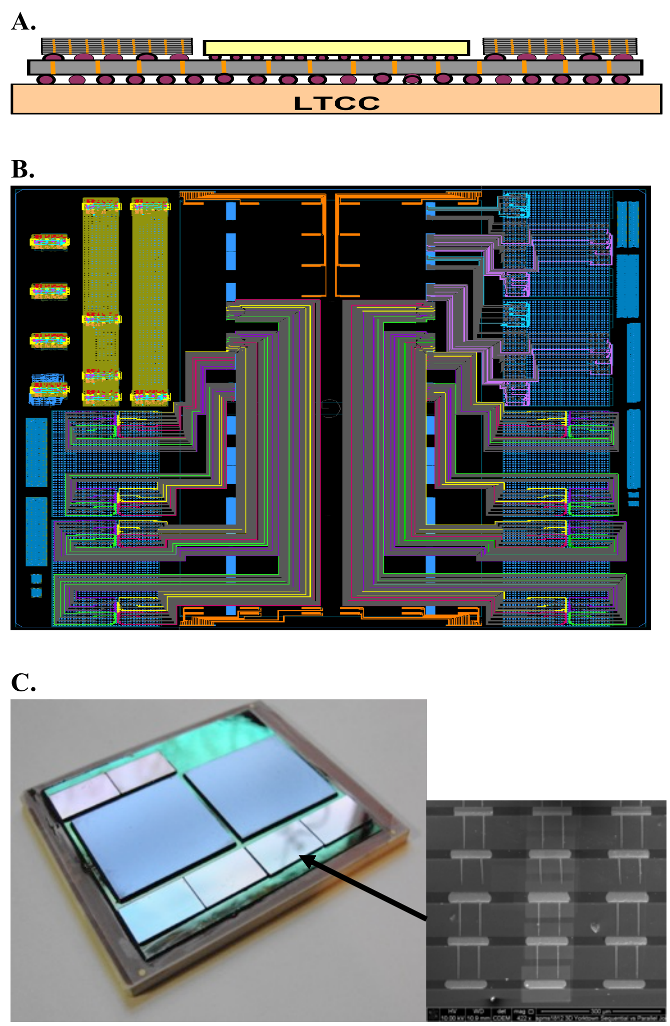


Figure 1 shows A. a schematic cross section of the test vehicle, B. one top down layer schematic of the Si package schematic and C. an assembled module showing base LTCC substrate at 50 × 60 mm with silicon package at 46 × 51 mm, large Si die with 50 μm pitch micro-interconnections and Si five high die stacks with 200 μm pitch interconnections between the approximately 50 μm thick silicon layers and the silicon package [11].

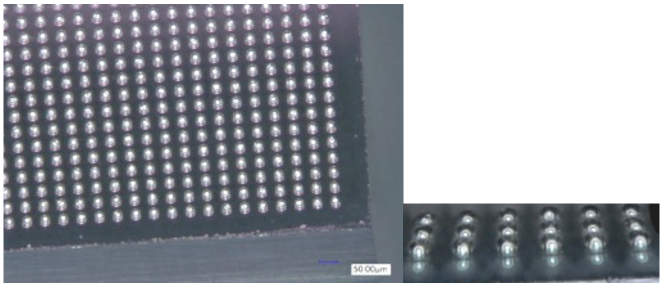


Figure 2 shows an example of the 50 µm pitch μC-4 on die for attach to the silicon package [11].

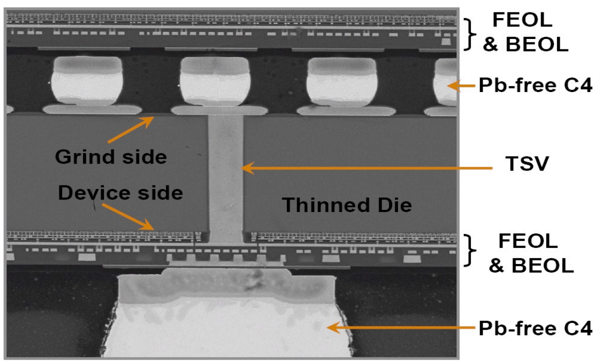
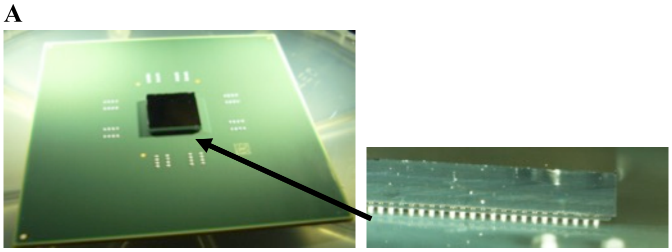


Figure 3 shows a scanning electron microscope cross section of a face to back die stack assembly using Cu TSV integrated into 25 µm diameter Pb-free interconnections between die strata levels for 45 nm active circuit die and assembled onto a laminate build up module using standard Pb-free C4 [12].

A



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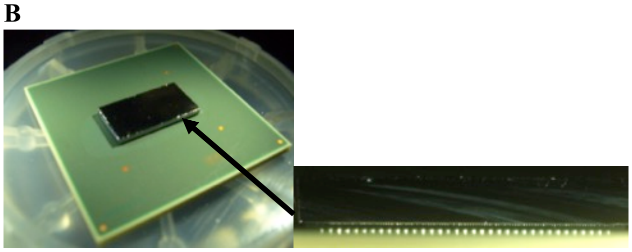
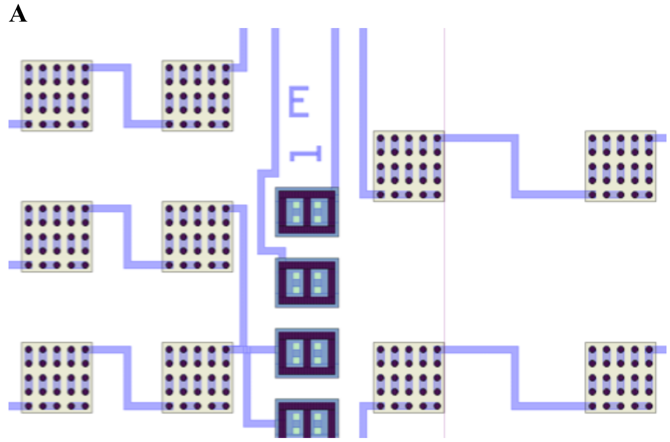


Figure 4 shows two assembled die stacks using active 45nm die with TSV's and 50 µm pitch Pb-free µC-4 interconnections assembled to organic build up substrates [13, 14].

Advancements in the precision handling technology have included improvements in the tools, materials, associated processes and an expanded range of application demonstrations. This current technology platform has supported hardware demonstrations for future applications including healthcare diagnostics, sensors and micro-systems, smart phones, IoT, high performance computing, artificial intelligence, advanced memory technology, micro-battery technology and heterogeneous system integration. Examples of these technology demonstrations come from precision handling of thin die, thin Si substrates and organic flexible substrates, thin components and sub-components for processing, singulation, assembly / integration and heterogeneous integration from 10's of components per wafer to 1,000,000's of components per wafer. Combinations of test vehicle design, build and integration and functional demonstrations continue using this growing family of tools and adhesives. Preliminary experiments have used chain link test vehicles with die and silicon or flex substrates to permit electrical characterization and structural cross sections of assemblies. For small X-Y size test vehicles using thin die, the X-Y die sizes ranged from ≤ 25 µm × 25 µm and 10 µm pitch I/O interconnections to thin die and X-Y sizes up to 400 µm × 400 µm sizes and I/O pitches included 10 µm, 20 µm, 50 µm, 100 µm, and 200 µm, respectively. **Figure 5** shows an example of one chip and corresponding substrate design having a 100 µm × 100 µm X – Y size, I/O pitch of 20 µm, and total die I/O of 25 area array interconnections. Other test

A



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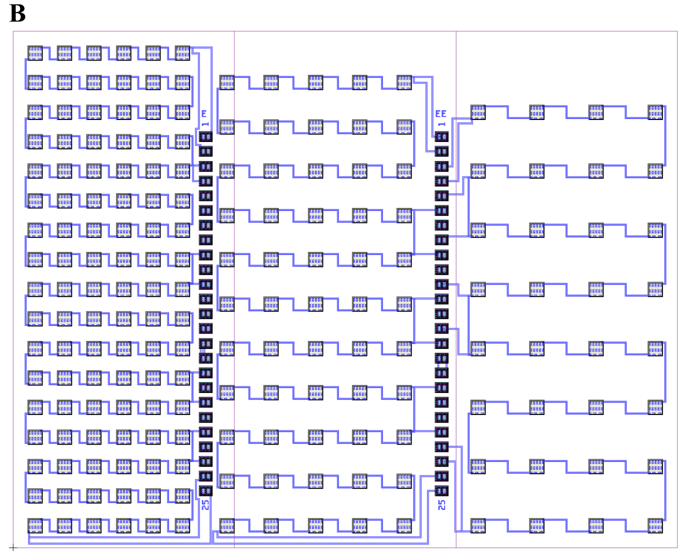


Figure 5 shows **(A)** a test vehicle chip chain link layout for a 100 µm × 100 µm die size with 20 µm I/O pitch having 25 I/O interconnections and **(B)** a corresponding substrate design that permits chain link electrical interconnection testing using a 1 × 25 test probe pad array with die pitch as 100um, 200um and 300 µm spacing.

vehicles and functional hardware have been fabricated for 30 μm to 50 μm thin die with die area measured from << $1mm^2$ to > $600mm^2$. The current small die size test vehicle builds have used the most recent IBM processes and IBM built (see **Figure 6**) and / or vendor built tools [15] used at either research or manufacturing sites. Similarly, use of IBM developed and / or vendor developed new and improved release layers and adhesives have been created and used in these studies. The new advancements support lower cost materials and low power laser, room temperature debonding still at less than 60 seconds per wafer. The release layer and adhesives support room temperature (RT) to 350C processing with semiconductor like chemical compatibility and post debonding cleaning. Multiple low cost adhesives and release layers were used in these studies. **Figure 7** shows an array of ≤ 50 μm thin, singulated die with < $1mm^2$ area fabricated using the glass or silicon handle wafers which support learning toward future healthcare and IoT applications. Typical thickness of components, die and substrates has been 30 μm to 50 μm however thickness demonstrations from ≤ 10 μm to ≥ 50 μm have been fabricated with this temporary handling technology.

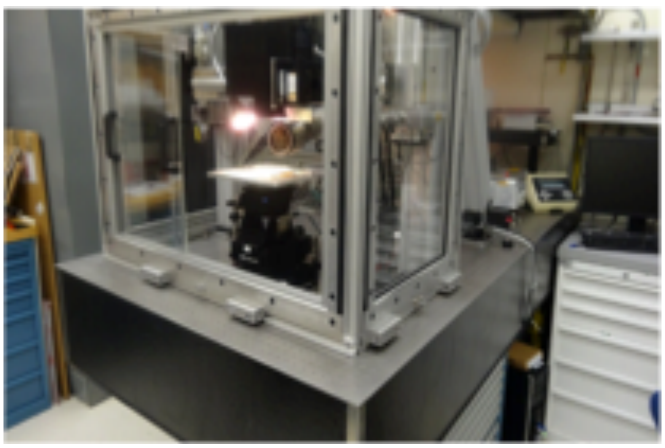


Figure 6 shows a scanning laser tool for room temperature debonding a handle wafer from the thin die, substrates or components.

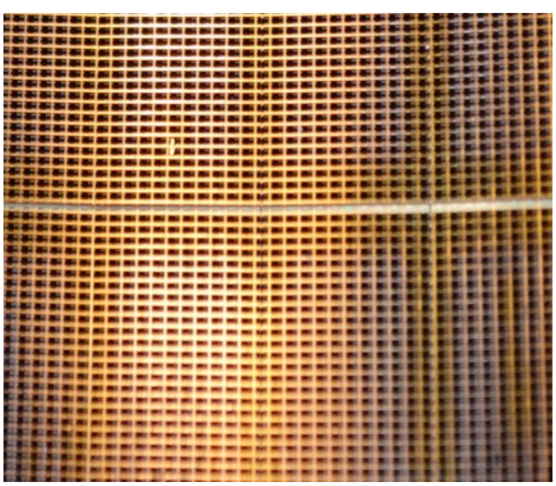
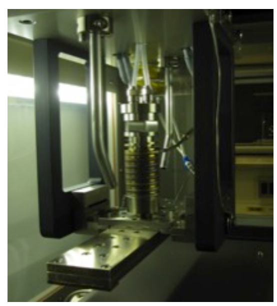


Figure 7 shows an array of ≤ 50 μm thin die with < $1mm^2$ area fabricated using the glass handle wafers.

B. Injection molded solder (IMS) technology

For many high I/O, fine pitch area array interconnection applications, plated underbump metallurgies and plated solder or plated micro-pillar and solder interconnections can be used. In prior wafer bumping demonstrations, IMS technology provided lead free solder bumps as reported in 2014 [16]. New examples of application features that can benefit from IMS technology include: precision composition control / flexible change to alternate compositions, void free solder interconnection, multi-size interconnection, multi-pitch interconnection I/O and solder bump interconnections for ceramic, glass or organic packages [17]. Additional IMS technology demonstrations have included area array interconnection fabrication of solder bumps or micro-pillars with solder interconnections from 15 μm diameter to ≥ 1000 μm diameter and through-silicon-via (TSV) / through-glass-via (TGV) solder via fill demonstrations. **Figure 8** shows an injection molten solder head for 200mm wafers and a wafer with varied bump diameters from 50 μm diameter to 500 μm diameter. **Figure 9** shows examples of solder and Cu pillar-solder bumps fabricated using IMS technology on substrates (Ceramic, Glass, and Organic Packages). Figure 10 shows flexible substrates with low temperature solder (LTS) bumps at 25 μm and 50 μm diameter bump size. Figure 11 shows IMS filled glass via of approximately 50 μm diameter and 300 μm depth.



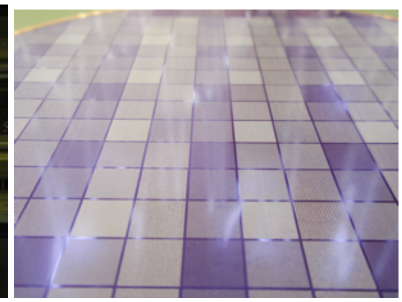


Figure 8 shows a IMS head for 200 mm wafer (left) and lead- free SAC 305 solder bumping result on an 200mm inch wafer with various size of pad opening from 50 μm to 500μm (right).

C. Precision micro-component, die, multi-die substrate and multi-component assembly / integration technology

Precision micro-component, die, multi-die substrate and multi-component heterogeneous assembly / integration for healthcare, IoT and AI Systems needs to support rapid prototyping and low cost, high volume manufacturing. Smart phones have been in used for more than a decade. Advancing healthcare sensors, wearables and IoT micro-systems can benefit from wireless electronics, sensors, antenna, batteries, micro-controllers, non-volatile memory devices and local data analysis as well as artificial intelligence to transfer critical trending data for specific applications. Precision data and calibration for the healthcare sensors is becoming more important. Future IoT applications are likely to drive high volumes and low cost as they become pervasive in an ever expanding set of applications. To help address these needs,

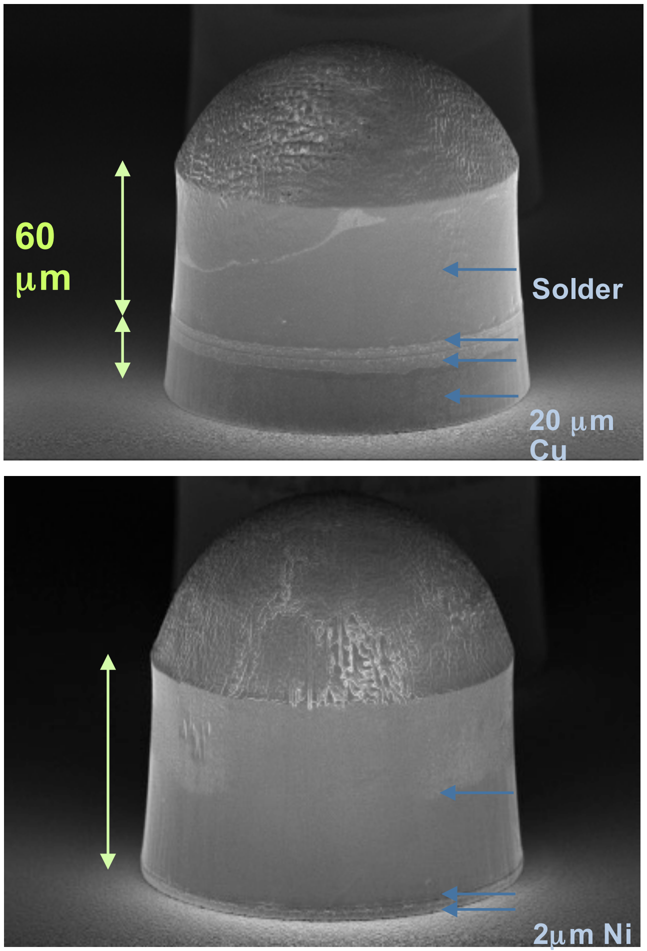


Figure 9 shows an IMS solder bump on underbump metallurgy on a copper pillar (Top) and solder on underbump metallurgy (Bottom), each after resist removal [16].

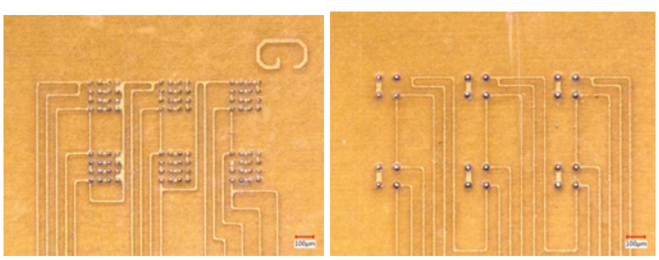


Figure 10 shows IMS low temperature solder (LTS) solder bumping result on a flexible substrate with 25 µm (left) and 50 µm (right) diameter solder mask opening.

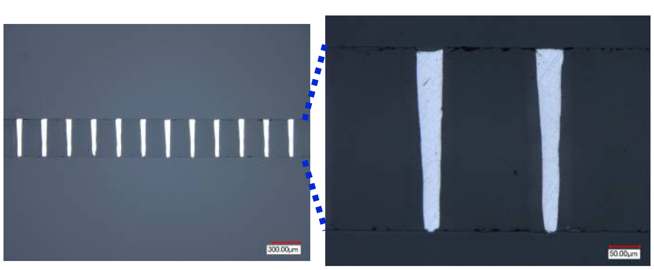


Figure 11 shows IMS filled Sn solder in through glass via of 50 microns diameters and 300 microns thickness.

the benefits of miniaturization, for ease of mobility, increased function in small form factors, lower cost, lower power and support to high volume manufacture may offer a path to realize these goals. Beginning with proper selection of micro-system architecture and continued heterogeneous integration for form factor scaling, use of compatible materials, processes and equipment may offer closure against these growing applications needs. **Figure 12** shows potential electronic elements that can support the micro-system architecture needed in many applications. **Figure 13** shows the relative volume of some micro-system demonstrators at IBM research that have been completed or are in progress comparing relative volume for systems from smart phones to healthcare, wearable and IoT sensors to future healthcare, wearable, and IoT sensors over time.

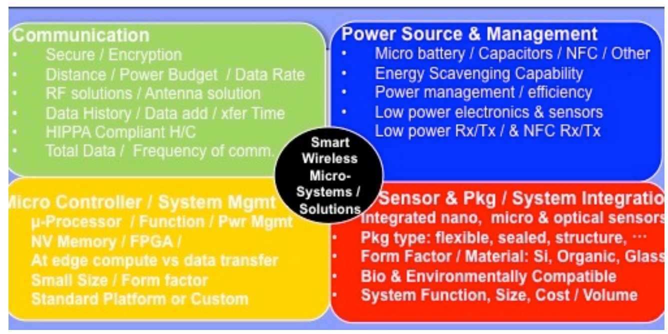


Figure 12 shows elements of a smart wireless micro-system architecture that could support communications, system control, power and sensing for healthcare, IoT with at the edge AI in small form factors.

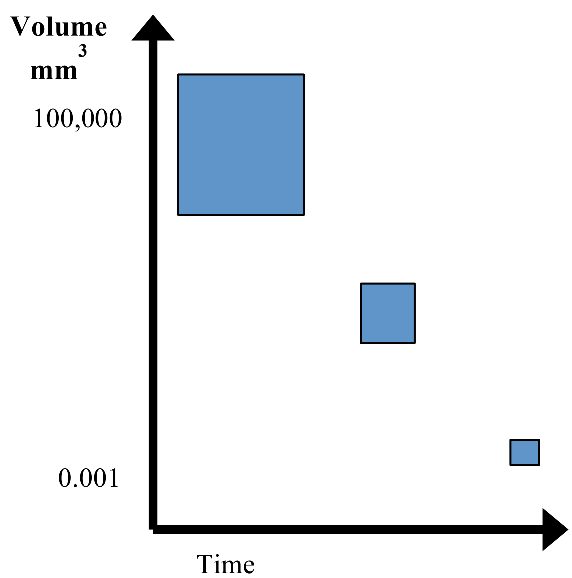


Figure 13 shows relative volume in mm^3 of systems from the smart phone (2007 to present), healthcare micro-systems, wearables and IoT sensor demonstrations at IBM Research (2012 to present) and next generation select healthcare micro-systems, wearables and IoT sensor demonstrations In progress (2015 to near future).

Wafer level and panel level fan-out packaging has provided a path for low cost high density packaging to compliment high density silicon die fabrication. As system solutions continue to leverage heterogenous integration into micro-systems with need of precision integration of multiple small size die, small components, sensors and packages, high speed and / or high-volume precision assembly and integration technologies are needed. For some healthcare, wearables and IoT applications, as the targeted micro-systems size decreases, precision integration solutions are needed that can both support component prototype build as well as support low cost, high volume manufacturing. Technology demonstrations that not only aide the fabrication of precision components or die in the 1,000's to 1,000,000's level per wafer or panel but also support precision assembly and integration process flow options have been under development.

The approach uses multi-chip precision assembly using wafer or potentially future panel level heterogeneous components and die integration into micro-systems. Examples of fabrication demonstrations for these components and systems are reported. New innovations and technology demonstrations have shown handling of thin and small die, substrates and components can be used for about 10 µm to 50 µm thick die of 25 µm × 25 µm to large die of > 25 mm × 25 mm to wafers of 200 mm or 300 mm diameter. Further demonstrations of multiple small die and components can be assembled into small healthcare and Internet of Things (IoT) sensors or systems in times of milli-seconds to seconds and thus provide the opportunity for high volume, low cost sensors and micro-system solutions using these heterogeneous integration compatible tools and processes, demonstrated at 360,000 units per hour [18]. Examples of these precision handling and assembly technology demonstrations are reported using single die, substrates, components, and for simultaneous hundreds or thousands of precision and controlled die and component assembly / integration. One example of a heterogeneous multi-die or component assembly and integration sequence is shown in **Figure 14** utilizing wafer level multi-die or component handling, precision placement and bonding, handle release, and die or component wafer removal and repeat with additional heterogeneous die, sensors, and components to create micro-systems.

Technology demonstrations of multi-die assembly are underway with die sizes to date from 25 µm × 25µm up to 400 µm × 400 µm. **Figure 15** shows an area view of die of 200 µm × 400 µm being simultaneously joined to a wafer of corresponding I/O interconnection substrates by using selective die level bonding, precision laser debonding and release. **Figure 16** shows a higher magnification photograph showing three 200 µm by 400 µm die bonding with micron level precision. **Figure 17** shows select 25um x 25um die removal to show an "IBM" pattern array from remaining die.

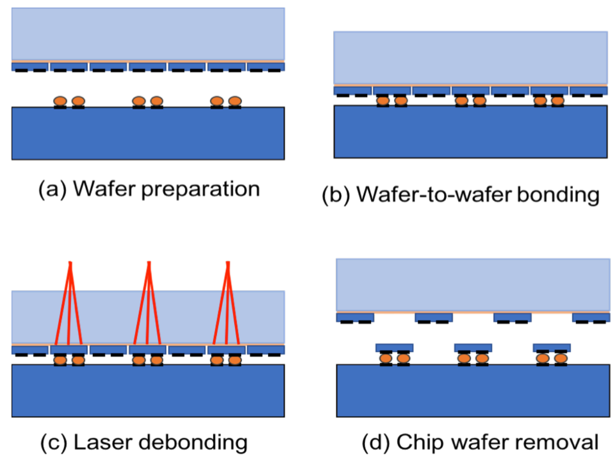


Figure 14 Process flow example for chip-to-wafer integration by programmable laser debonding technology: (a) wafer preparation: thin top chips on handler wafer and bumps on substrate wafer, (b) wafer-to-wafer bonding, (c) programmable laser debonding, (d) chip wafer removal. Integrate heterogeneous die, …etc.

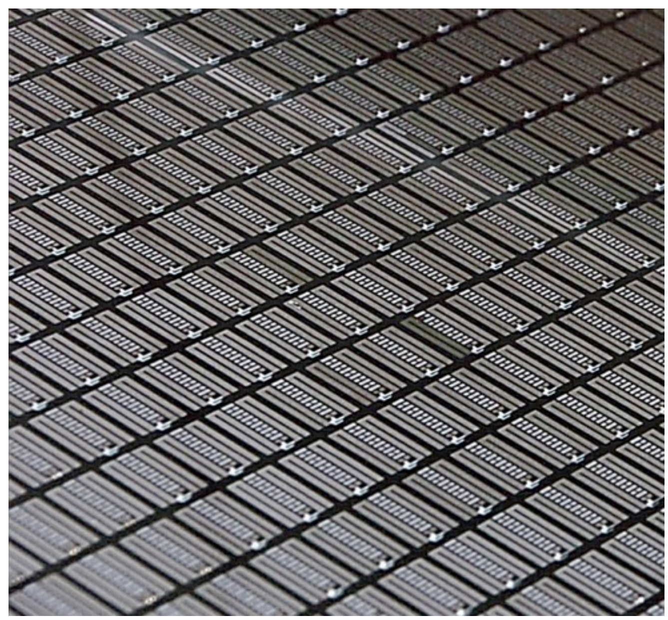


Figure 15 shows a substrate wafer with precision joining of multiple small die of 200 µm ×400 µm size.

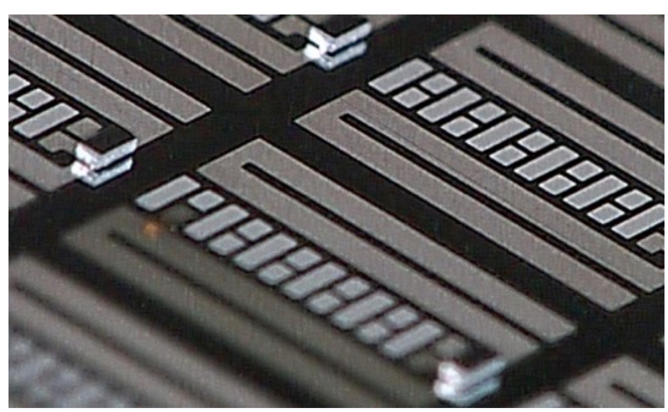


Figure 16 shows a substrate wafer with 3 thin 200 µm × 400 µm die joined using solder interconnections.

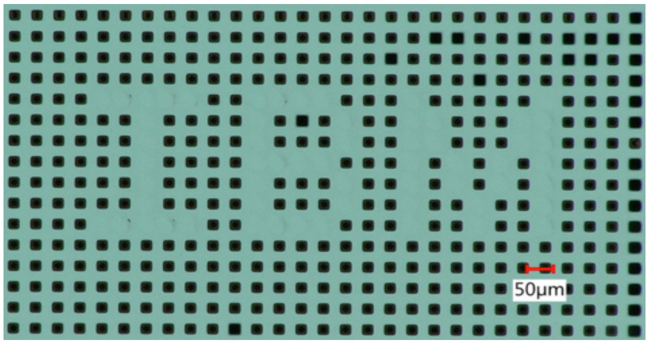


Figure 17 shows select 25um x 25um die removal to show “IBM” pattern.

D. Precision laser micro-machining, cutting and welding technology

IBM has also developed precision laser tools for micro machining, cutting and welding. These tools along with experiments on materials and compatible processes have led to technology demonstrations that support next generations of healthcare and IoT microsystems and sensors. Unique beam position, size and calibration technology leveraging high speed Micro, Nano or Pico-second, solid state scanning lasers and programming flexibility permit rapid prototyping and utilization on a wide range of technology, healthcare, and IoT application demonstrations. Examples of high speed micro-machining and cutting for precision micro-component and micro-substrate fabrication are reported.

One laser system used a high-power output picosecond UV laser source with a lens system to control the beam path. The choice of the light source is optimal for bombarding the molecules for abrasion of the material without exciting lattice vibration modes, and thus minimize the heating effect. The mechanism for this system is believed to be "cutting" and "milling" away the targeted material rather than "melting" or “ablating” the material. **Figure 18** shows an experimental demonstration in a cutting mode of operation where the spot size at typical operation power level can be set to a 15 μm to 25 μm diameters (25 μm diameter in this experiment) and the cutting precision can achieve ≤ 5 μm accuracy.

Figure 19 shows the laser system that can be used for both cutting and milling purpose. The system can cut through 700 um full thickness Si wafer if needed but is more efficient for applications including thin chip dicing, cutting, micro-milling and micro-machining. Cutting and milling demonstrations have been successful with metal, plastic, polymer, silicon, glass, and paper. **Figure 20** provides an example of metal laser micro-milling while **Figure 21** provides an example of precision patterning of a flexible substrate. **Figure 22** shows the laser system cutting a glass substrate.

E. Flexible multi-channel, micro-fluidic systems for smart sensing, point of care (POC)

In addition to the integration of electronics components to a thin and or flexible substrate by 2D or 3D integration, microfluidic components and sensors can be fabricated and integrated as a compact bio sensor system or diagnostic lab on a chip or flex substrate for personalized health monitoring. Passive microfluidics for bio-sensing applications can enable routine, low-cost, and non-invasive health monitoring using a variety of bodily fluids. In their simplest form, a liquid is drawn through fine channels on a test strip by surface tension, where reagents are added, mixed, and then the sample is analyzed using either electro-chemical or optical measurements.

An image of a microfluidic test strip with an integrated electrochemical sensor is shown in **Figure 23(A)**. From right to left, it consists of the fluid inlet port, delay lines, reagent mixing chambers, mixing line, a detection chamber with integrated electrodes for chemical or impedance based biomarker detection, and electrical contacts for the readout electronics. The channel configuration and surface property

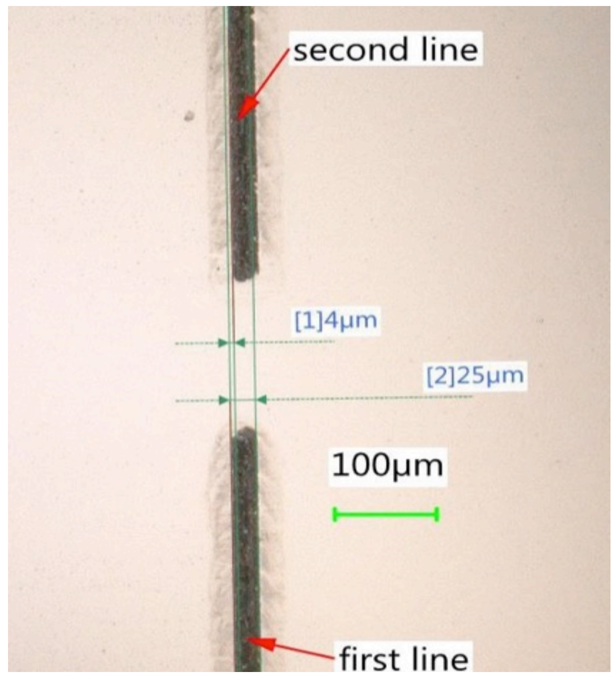


Figure 18 shows a first line is marked on a piece of Si wafer at a random location, and the system use a vision recognition module to find the first line then mark the second line as an extension. From the image, we can see that 1) the width of the marking is 25 μm, corresponding to the laser spot size at the marking power level; 2) the shift between the first line and the second line is 4 μm, which is a measurement of the combined accuracy of the vision recognition module and laser positioning module.

Figure 19 shows the laser cutting & milling equipment

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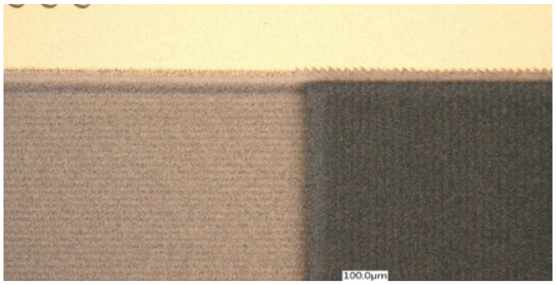

B

Figure 20. (A) shows controlled removal of 0.1 µm thickness of metal deposited on top of a Si wafer and (B) shows milling with a finer resolution with a reduction in line scan width from 15 µm to 5 µm.

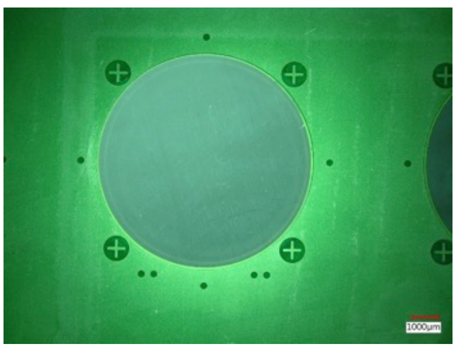

Figure 21 shows patterning on a flexible substrate.

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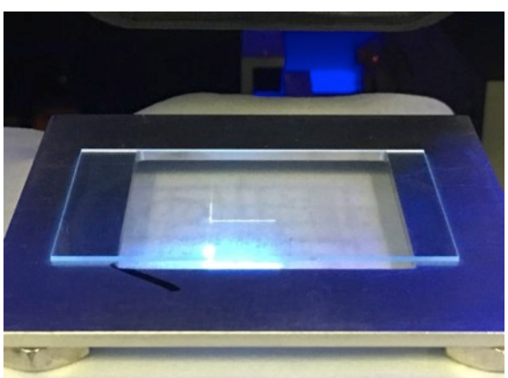

Figure 22 shows the laser system cutting a glass substrate.

are designed and treated to ensure sufficient capillary pressure to drive the test fluid though the device from inlet to mixing chamber to testing chamber. Columnar posts are arranged in the mixing chamber to drive the fluid though the middle of the chamber while the peripheral is corrugated to slow down the flow at edge to minimize air trapping. The vent lines contain stop gates to restrict the fluid flow and allow time for the reaction with the reagent in the detection chamber to complete. The test strip is fabricated on a polyester film (PET) by first depositing and patterning the metal electrode on the substrate, **Figure 23(B)** and then an epoxy based dry film resist is laminated and patterned to form the microfluidic channels [19, 20], **Figure 23(C)**. Prior to the lamination of the cap layer, **Figure 23(D)**, reagent(s) are deposited in the mixing chamber and the electrode surfaces are functionalized to capture a specific biomarker. It is important when selecting the materials for such a microfluidic device that the surface wetting properties are appropriate and are stable after device fabrication. Such device or multiple of the devices can be used for wearable sensors or integrated on to a medical device or appliance to monitor one or more biomarkers.

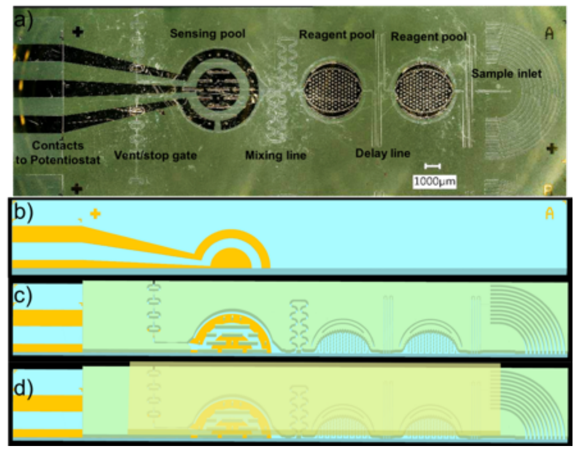

Figure 23. Image **(A)** and oblique sectional schematic of microfluidic device build sequence **(B, C & D).**

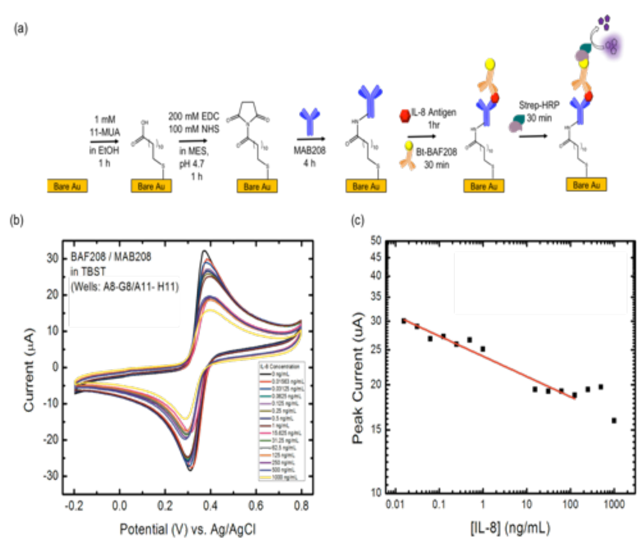

Figure 24. **(A)** Schematic for IL-8 antibody immobilization onto Au substrates via EDC/NHS coupling for specific binding of IL-8. **(B)** Cyclic voltammograms measured on an IL-8 functionalized electrode to detect varying concentrations of IL-8. **(C)** Peak current at E=0.35V plotted as a function of IL-8 concentration.

One example of the application of such device is electrochemical sensing of Interleukin 8 (IL-8), which is a key mediator associated with inflammation. IL-8 has been implicated with inflammation, obesity, cystic fibrosis, and colorectal cancer. **Figure 24** shows a schematic for IL-8 antibody immobilization on to Au substrates via EDC/NHS coupling.

A metal-coated polyester (PET) substrate was immersed in a solution of 11-mercaptoundecanoic acid (11-MUA) to form a self-assembled monolayer (SAM) followed by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS) treatment to generate a reactive ester at the terminus of the SAM. The substrate will be exposed to an aqueous solution containing a monoclonal IL-8 antibody (MAB208). The chemical reaction insures that MAB208 is covalently attached to the substrate surface via amide bond formation between the primary amine group on MAB208 and the reactive ester of 11-MUA. A biotinylated secondary antibody (Bt-BAF208) is used to sandwich the IL-8 antigen, followed by binding of a streptavidin-bound horseradish peroxidase (HRP) enzyme. Detection is observed spectrophotometrically at 450 nm in the presence of 3,3',5,5'-tetramethylbenzidine (TMB), a 1:1 substrate to HRP **(Figure 24(A). Figure 24(B)** is a cyclic voltammogram measured at varying concentrations of IL-8 in tris-buffered saline with Tween 20 (TBST). **Figure 24(C)** shows plots the peak current at E = 0.35V as a function of IL-8 concentration. Further optimization of the antibody concentrations is required to improve the overall signal and sensitivity of IL-8 detection. The surface functionalization scheme can be integrated with microfluidic device as a bio-sensor to sense the IL-8 concentration in body fluid.

F. Small form factor micro-systems and energy solutions / technologies

Small form factor healthcare sensors & micro-systems, POC diagnostic systems and IoT systems require energy solutions that meet the targeted application requirements. New generations of energy solutions from small micro-batteries and small capacitors to super capacitors and energy scavenging solutions to externally supplied energy recharging or powering solutions provide energy solutions for micro-systems and sensors.

New flexible micro-systems using ultra-thin sensors have been demonstrated [21] and reported at the IEEE International flexible electronics technology conference in 2018. These new sensors along with other sensors are being applied to chronic disease monitoring such as Parkinson Disease and for healthcare monitoring for activities of daily living.

Demonstrations of novel miniaturized healthcare sensors and systems are being combined with data streaming, algorithms and AI to provide insights for quality of life improvements.

III. SUMMARY

Innovations, electronics, diagnostics, algorithms and AI are being applied to healthcare and IoT applications toward chronic disease guidance and higher quality of life. Some benefits have already been realized and the journey to leverage advancing technology holds the promise for future changes that provide diagnostics, data trending and machine learning at personalized level for individual guidance with longer life. Heterogeneous integration is being applied to healthcare and IoT for future novel sensors and diagnostics.

IV. FUTURE WORK

Healthcare POC diagnostics and sensors are being developed that offer the opportunity for earlier disease detection, disease delay or prevention for improved quality of life. Heterogeneous technology is being applied to create high performance micro-systems for Healthcare and IoT future solutions.

Look for upcoming 2018 and 2019 publications on diagnostics and healthcare sensors that provide unique insights in healthcare diseases. Also look for base technology advancements in micro-batteries and microsystem heterogeneous integration solutions that support prototyping and future volume manufacturing.

Also look for expanded intellectual property technology platforms in each area reported in this publication.

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REFERENCES

[1] 1. P. Roy, R Tennakoon, K. Cao, S. Sedai, D. Mahapatra, S Maetschke, R. Garnavi, "A novel hybrid approach for severity assessment of diabetic retinopathy in colour fundus images", to appear in the proceeding of The 2017 IEEE International Symposium on Biomedical Imaging.

[2] S. Sedai, R Tennakoon, P. Roy, K. Cao, R. Garnavi, "Multi-stage segmentation of the fovea in retinal fundus images using fully convolutional neural networks", to appear in the proceeding of The 2017 IEEE International Symposium on Biomedical Imaging.

[3] https://www.ibm.com/blogs/research/2017/04/spotting-diabetic-retinopathy/

https://www.ibm.com/blogs/research/2017/10/computers-to-aid-melanoma-detection/

https://www.ibm.com/blogs/research/2017/12/ai-epileptic-seizure-prediction/

[4] www.ibm.com/blogs/think/2016/10/sharpless

[5] M. A. Rapsomaniki et al., "CellCycleTRACER accounts for cell cycle and volume in mass cytometry data", *Nature Communications* **volume 9**, Article number: 632 (2018)

[6] Ruhong Zhou et al., Science 2018.

[7] T. Chan and coworkers, New England Journal of Medicine 2014, 371, 2189-2199.

[8] http://science.sciencemag.org/content/early/2017/12/06/science.aao4572

[9] P.S. Andry et al., "Advanced Wafer Bonding and Laser Debonding," Electronic Components and Technology Conference 2014.

[10] B. Dang et al., "Feasibility Study of Si Handler Debonding by Laser Release," Electronic Components and Technology Conference 2016.

[11] J. U. Knickerbocker et al., "2.5D and 3D Technology Challenges and Test Vehicle Demonstrations," Electronic Components and Technology Conference 2012.

[12] M. Farooq et al., "3D Copper TSV Integration, Testing and Early Reliability," IEDM 2011.

[13] Y. Liu et al., "A Compact Low-Power 3D I/O in 45nm CMOS," ISSCC 2012.

[14] M. Wordeman et al., "A 3D System Prototype of an eDRAM Cache Stacked over Processor-like Logic using Through Silicon Vias," ISSCC 2012.

[15] Multiple patents, know-how and / or technology specifications licensed from IBM Corporation.

[16] J. W. Nah et al., "Wafer IMS (Injection Molded Solder) –A New Fine Pitch Solder Bumping Technology on Wafers with Solder Alloy Composition Flexibility", Proc. IEEE 64th Electronic Components and Technology Conference, May 2014, pp. 1308-1313.

[17] J. W. Nah et al., "Injection Molded Solder (IMS) technology for solder bumping …," ECTC 2018.

[18] Q. Chen et al., "High-speed Precision Handling Technology of Micro-chip …," ECTC 2018.

[19] Y. Temiz, E. Delamarche, J. Micromech/ Microeng. **24** (2014) 097001

[20] J. Tirapu-Azpiroz, Y. Temiz, E. Delamarche, Biomed Mecrodevices (2017) 19:95

[21] K. Sakuma et al., "Flexible Piezoresistive Sensors Fabricated by Spalling Technique," International Flexible Electronics Technology Conference 2018.