

Medical Metrology in Australia.

Lack of quality control of physical medical measurements in Australia

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Target audience

This document is written for both clinicians and metrologists.

Summary

When we fill our car at the petrol pump, we trust that the meter on the pump indicates the correct quantity of fuel we purchase. When we buy a kg of potatoes we trust that the greengrocer's scale is in error by no more than a few grams. In most cases our trust is not misplaced — national regulations supported by an extensive international measurement framework provide quality assurance, laboratory accreditation and traceability for trade and many other measurements that are important to society, including industrial, and scientific measurements. It is very strange, therefore, that while we can trust the meter on the petrol pump and the scale in the greengrocer, we unfortunately can't place the same degree of confidence in the sphygmomanometer in our GP's office, the spirometer in the respiratory physician's clinic or the optician's tonometer. In Australia, measurements for trade have a pedigree that is traceable to the National Measurement Institute in Lindfield NSW and thence to the International Bureau of Weights and Measures (BIPM) in Paris. This traceability means that kilograms, litres and other units in Australia are, within well defined uncertainties, equal to the corresponding units across Australia and in France and most other industrialised countries. Most physical medical measurements, however, don't participate in the international metrology framework, and therefore are not traceable and cannot be trusted to the same extent. In Australia the quality control over the distribution of potatoes is substantially better than the quality control that underpins the prescription of antihypertensive drugs.

All medical devices distributed in Australia have to be registered with the TGA which also regulates the manufacture of medical devices in Australia. Assessment of quality and fitness for purpose of medical instruments is the responsibility of the manufacturer or 'sponsor' and evidence of this evaluation is submitted to the TGA for approval. Once an instrument is registered, however, management of the performance of medical instruments is not regulated and is left to the discretion of users. For example, low cost aneroid sphygmomanometers, which are well known to be unreliable, can be used for decades without ever being checked or calibrated. Medical device manufacturers are required to report adverse events involving their devices to the TGA, but erroneous measurements, if detected, do not appear to constitute adverse events.

Medical errors are a recognised cause of harm in the health care system, but clinical measurement errors are seldom, if ever, identified as causes of adverse events. There is, however, strong evidence in the literature that clinically significant systematic errors are common in physical measurements such as blood pressure, intraocular pressure, and pulmonary function. In Australia it is likely that tens of thousands of adults have been incorrectly diagnosed as hypertensive and are needlessly suffering from the psychological effects of the 'hypertension' label and the physiological side effects of antihypertensive drugs. It is also likely that a similar number of hypertensive adults are not treated and are therefore at increased risk of cardiovascular disease. Much less is known about the sensitivity of diagnoses to errors in other physical measurements such as intraocular pressure, spirometry and ECG.

All medical testing laboratories and many medical imaging facilities are externally accredited. Many health care providers are externally accredited or are members of colleges. Further accreditation for health care providers is under consideration in Australia. Physical measurements made by clinicians and medical technicians in Australia, however, are not subject to regulated quality control and many clinical measuring instruments are not adequately maintained and calibrated.

Quality control of physical measurements in medicine in Australia is substandard compared with other measurements that are important to society, such as measurements for trade and industry. Australia lags behind many other industrialised countries in medical metrology. There is a clear, unmet need to integrate physical medical measurements with the existing international measurement framework to improve the trustworthiness and inter-device variability of measurements. The health care system, however, is very sensitive to increasing costs. Therefore there is also a need for multidisciplinary research to investigate and quantify the impacts of inadequate quality control on health care, to identify areas of greatest need, and estimate the costs and benefits of integrating clinical measurements with the international measurement framework. Quality control may increase costs of measurements but reduction in systematic errors and inter-device variability will improve detection, treatment and follow-up of disease and hence reduce overall health care costs and improve outcomes.

Background

Martin Turner is an electrical engineer with a PhD in Biomedical Engineering (respiratory measurements in mechanically ventilated infants). Between 1979 and 1997 he worked as a senior biomedical engineer in a large public hospital, and lectured instrumentation and measurement to undergraduate and postgraduate engineering students and anaesthetists. He also gained experience in physiological measurements and mathematical modelling of human thermoregulation. In 1998 he joined the University of Sydney, participating in research in the measurement and modelling of cardiac output, cerebral perfusion and anaesthetic uptake. With one foot in industrial and scientific measurement and metrology, and the other in medical research (mainly physiological measurement), he became acutely aware of major discrepancies between the way measurements are made in the two fields. His interest in medical metrology started 1997. While teaching engineering students the importance of quality control, traceable calibration and uncertainty analysis in measurement, he observed clinicians making measurements every day with unmaintained, inadequately calibrated instruments. In 2003 he was invited by the Chief Metrologist of Australia to speak to the National Measurement Laboratory (now the National Measurement Institute) on Metrology in Medicine. Since then a major part of his research effort has been directed at quantifying the effects of inadequate quality control and random variability on diagnosis of disease, focusing on measurement of blood pressure and detection of hypertension.

Martin Turner has published 42 articles in international peer-reviewed medical and biomedical engineering journals. He has consulted to industry in the fields of measurement, medical engineering and metrology. He is a technical assessor for the National Association of Testing Authorities (NATA) in the field of Measurement Science and Technology and a member of the Metrology Society of Australia.

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Introduction

Modern healthcare relies to an ever increasing extent on quantitative measurements. Many of these measurements are made on blood and tissue samples in externally accredited medical testing laboratories where great care is exercised to control the quality of the measurements.¹⁻³ However, a rapidly increasing number of measurements, mostly physical measurements, are made in clinicians' offices, patients' homes, nursing homes, hospital wards, intensive care units and operating theatres where quality control is sometimes less than thorough or even non-existent. Diagnosis, treatment and follow up often depend strongly on the accuracy of these physical measurements, and it is important that quality control is adequate.

Measurements that are important to society such as the volume of petrol delivered at service stations and the weight of vegetables dispensed by greengrocers are subject to regular verification checks as required by Australian National Measurement Regulations.⁴ An extensive international measurement framework provides quality assurance, traceability and laboratory accreditation for many measurements, including industrial, scientific and trade measurements, medical imaging and medical laboratory testing. Quality control of medical devices that perform physical measurement functions, however, is not regulated and depends entirely on the clinician or the institution in which the clinician works. It is extraordinary that while we can usually trust the meter on the petrol pump and the scale in the greengrocer, we unfortunately can't place the same degree of confidence in the sphygmomanometer in our GP's office, the respiratory physician's spirometer, or the optician's tonometer. In Australia at present there is better quality control over the distribution of potatoes and onions than over the measurements that underpin prescriptions of antihypertensive drugs and inhaled corticosteroids.

There are costs and inconveniences associated with the implementation of quality control procedures. Traceable calibration and regular in-house checks may appear to be costly and time-consuming. While medical instruments are being checked or calibrated they are not available for use, so some duplication may be necessary. Some clinicians are of the opinion that there may be little benefit in regular traceable calibration of medical measuring instruments. Many medical practitioners appear to assume that the biological variability that is inherent in many medical measurements lessens or even removes the need for good quality control of measuring equipment.

If 'Australian Medical Measurement Regulations' were to be written, at present there is very little metrologically sound evidence available to inform the setting of performance requirements such as uncertainties, calibration intervals and other aspects of quality control of many medical instruments. Further, much of the infrastructure such as commercial and national calibration facilities required to support quality control of medical measurements does not exist in Australia. At present the benefit-cost ratio of good quality control of medical measuring devices is not clear, neither to clinicians nor to those who write the guidelines and regulations.

Here I describe some of the defects in current clinical measurement systems and how these defects likely harm patients. I show that there is a clear, unmet need in Australia and other countries to incorporate physical medical measurements in the international traceability framework to lift quality to the standards that pertain to medical laboratory measurements and other measurements that are important to society such as those in science, industry and trade. There is a need for multidisciplinary research to investigate and quantify the impacts of the defects on health care and estimate the costs and benefits of integrating clinical measurements with the international measurement framework.

Background

Random errors, systematic errors and biological variability

Measurement errors can be systematic, random, or, more commonly, a combination of the two.⁵ Pure random errors are distributed around zero and have zero mean. The probability density function of random measurement errors is commonly, but not always, Gaussian. Random measurement errors can almost always be reduced by averaging or filtering. Intra-individual biological variability is usually random, although under some circumstances, for example circadian variation, has a systematic component. In most medical measurements random measurement error and random biological variability are difficult to separate.

Systematic errors, sometimes referred to as 'bias', have non-zero mean and are approximately the same magnitude and sign in each measurement.⁵ Common causes of systematic errors include inadequate

calibration, instrument drift, nonlinearities and external effects such as changes in ambient temperature, barometric pressure, humidity and battery state. It is possible for systematic error caused by, for example, changes in calibration, to cause variability in measurements that appears to be random. For example if the gain of the flow meter in a spirometer drifts up and down due to accumulation of moisture and occasional cleaning,⁶ and is used to measure a patient's lung function at monthly intervals, the changes in the calibration curve caused by moisture and cleaning may cause apparently random changes in peak flow, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC). In some situations, for example clinical studies in which measurements made in the same way by the same instrument are compared between groups or before and after treatment, systematic errors of limited magnitude may not significantly affect study outcomes. If guidelines or thresholds for diagnosis and treatment are derived from these studies, however, these errors may be critical.

The effects of systematic errors on detection of disease

Diagnostic errors are the single largest contributor to ambulatory malpractice claims in the USA.⁷ An important effect of systematic error on clinical outcomes is in detection of disease, particularly when threshold values are used for diagnosis. For most physical medical measurements the sensitivity of disease diagnosis to systematic measurement errors is not well known. However, the sensitivity of diagnosis of hypertension to systematic error in blood pressure (BP) measurements has been studied.⁸ Turner and colleagues showed that detection of hypertension is very sensitive to systematic error in BP measurements.⁸ For example, a clinician who assesses BP in 100 new adult patients, might diagnose, on average, 25 with systolic hypertension contributing to high risk of cardiovascular disease, and start those patients on antihypertensive treatment. If the clinician's sphygmomanometer systematically under-reads by 5 mm Hg, however, only 17 of the 25 hypertensive patients would be identified and eight hypertensive patients may be missed.⁸ The sensitivity of hypertension detection to systematic errors in BP measurements has been studied further by Monte Carlo simulations that included the effects of biological variability,^{9 10} and the results are consistent with the original 2004 study.⁸ There is some evidence that systematic errors permitted by present sphygmomanometer standards¹¹⁻¹³ are excessive and that standards should be tightened.^{8 10} Many studies have shown that the quality control of sphygmomanometers in clinical use in Australia and other countries is inadequate.¹⁴⁻²²

Physical medical measurements in Australia

In 2007 there were 62,652 medical practitioners employed in Australia, of whom 24,121 were primary care practitioners.²³ In the 2008–2009 financial year 140.3 million patient-practitioner encounters took place and 100.4 million laboratory tests and five million Medicare-funded diagnostic procedures and investigations were conducted.²⁴ The problem most frequently managed by general practitioners was hypertension which was dealt with at 10.1% of encounters.²⁵ Blood pressure is also commonly measured during encounters for other problems, so it is likely that BP is the measurement most commonly made in clinical practice. Other common diagnostic procedures and investigations performed during the 2008–9 financial year included respiratory (482,000 per year– mainly spirometry), ophthalmological (422,800 per year– mostly perimetry), optometry (6.4 million per year– vision and intraocular pressure tests) and cardiovascular (2,600,000 per year– mainly ECGs).²⁴

Quality management in medical testing labs

Management of quality in medical laboratories in Australia improved substantially in 1983 when external accreditation of laboratories began. Only accredited laboratories can claim Medicare payments. The National Association of Testing Authorities (NATA) accredits medical testing laboratories to the international standard ISO 15189 *Medical Laboratories - Particular requirements for quality and competence*.^{1 26} As of August 2010, 615 Medical testing laboratories are accredited. ISO 15189 is closely related to ISO 17025,²⁷ the standard to which industrial calibration laboratories are accredited, and ISO 9001,²⁸ a general quality standard to which many organisations are certified. ISO 15189 requires medical laboratories to operate a quality management system similar to that required by ISO 9001. Laboratory quality management systems are required to include procedures to review contracts, control documents, identify and control nonconformities with the quality systems and take corrective actions. Internal audits have to be carried out regularly and records of all activity related to both administrative and technical quality (e.g. traceable calibrations) have to be kept for predetermined times. Technical requirements of the standard concentrate on

personnel, laboratory accommodation and equipment. Personnel are required to be competent and to undergo training specific to quality assurance. Environmental conditions in the laboratory have to be carefully controlled and monitored. Equipment has to be fit for purpose and regularly maintained and calibrated using traceable reference materials. Calibration procedures have to be documented and performance criteria such as uncertainties of measurement estimated. Laboratories are required to participate in inter-laboratory comparisons. When errors are detected clients have to be informed. Pre- and post-analytical procedures for handling samples have to be carefully designed and fully documented. Medical laboratories in most industrialised countries are accredited to the same standard. Many laboratories also operate additional quality management systems such as Six-Sigma and Total Quality Management (TQM),²⁹ or are certified to ISO 9001.²⁸

Despite considerable efforts to control the quality of laboratory measurements, errors still occur at rates as high as one in every 214 laboratory results.³⁰

Medical errors

Avoidable medical errors are a significant cause of morbidity and mortality. An estimated 44,000–98,000 people die each year as a result of medical errors in hospitals in the USA.³¹ The Quality in Australian Health Care Study³² reported that 18,000 (95% CI 12,000–23,000) patients died in Australian hospitals in 1992 as a result of preventable errors. A further estimated 50,000 and 280,000 suffered permanent and temporary disability respectively.³² In a 2005 editorial, Wilson and Van Der Weyden suggested that the safety of healthcare in Australia had not improved in the ten years between 1995 and 2005.³³ It is likely that many more errors occur in out-patient settings than in hospitals.³⁴ In a cross-sectional survey conducted in North Carolina USA in 2008, 15.6% of 1697 ambulatory patients responded that a physician had made a mistake associated with their care in the previous 10 years.³⁵

At present health care providers in Australia are not required to be accredited, although most specialists cannot practice unless they are fellows of the corresponding College. Many general practitioners are not Fellows of the Royal Australian College of General Practitioners (RACGP). Various quality standards for health care providers are in use at present. The RACGP publishes a Standard for General Practice against which GP practices can choose to be accredited by third party accrediting organisations. Some GP practices are certified to ISO 9001 (2008),²⁸ some are accredited to *Core Standards for Safety & Quality in Healthcare* and some to the older *Private Sector Quality Criteria*.

In recognition of the need to reduce the incidence of preventable errors, the Australian Federal Government established the Australian Commission on Safety and Quality in Health Care in January 2006 to 'lead and coordinate improvements in safety and quality in health care in Australia'. It intends to achieve this objective in part by recommending 'nationally agreed standards for safety and quality improvement'. In November 2009 the Commission released a consultation paper seeking comment on a proposed system for safety and quality accreditation of all health care facilities in Australia. The Commission is thus following the example set by the medical laboratory community in opting for external accreditation to improve quality.

Management of quality of measurements that are important to society

Accuracy of measurement is very important in science and industry, and for international, national and retail trade. Every time we buy food, open a tap, turn on a light or put fuel in a vehicle we are placing our trust in a measurement system. Making physical measurements that can be trusted requires:

- instruments of design appropriate to the task and of adequate quality and robustness,
- proper maintenance, regular, traceable calibration of instruments and regular on-site checking of instruments, and
- properly trained operators who have adequate experience in the correct use of the instrument.

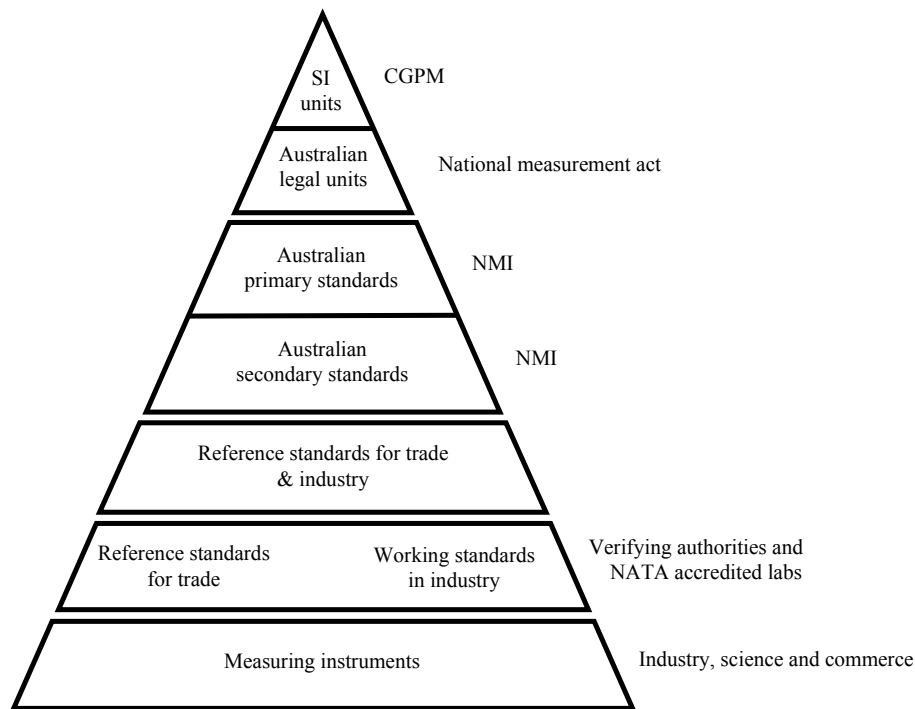


Figure 1. The hierarchy of standards by which physical measurements are related through the national and international metrological pyramid to SI units. NMI: National Measurement Institute; CGPM: General Conference on Weights and Measures; SI: International System of Units.

Trade and industry

Before the international measurement framework matured, scientists, industrialists and business people had to make their own individual arrangements to ensure that their measurements and the measurements of others on whom they depended were of adequate accuracy. In 1875 an international treaty, the ‘Convention of the Metre’, was negotiated by 17 countries. This treaty created the International Bureau of Weights and Measures (BIPM), an intergovernmental organization under the authority of the General Conference on Weights and Measures (CGPM), based in Paris. The BIPM acts in matters of world metrology, particularly concerning measurement standards and the need to demonstrate equivalence between national measurement standards. The BIPM now has fifty-four Member States, including all the major industrialized countries. Australia signed the treaty in 1947 and is represented on the CGPM.

The international framework by which a physical measurement can be related back to the relevant SI unit is known as traceability (Fig 1). The National Measurement Act of Australia requires the National Measurement Institute (NMI, a division within the Federal Department of Innovation, Industry, Science and Research) to maintain standards for measurements of physical and chemical quantities. International traceability is achieved by collaborating with both national standards laboratories of other scientifically advanced nations and with the BIPM through inter-comparisons of national standards. These inter-comparisons provide confidence in the consistency of the international measurement system. Reference standards are disseminated to science and industry by commercial calibration laboratories accredited by the National Association of Testing Authorities (NATA).

The process of ensuring that the design of instruments is appropriate to the task and instruments are of adequate quality and robustness is termed ‘pattern approval’ or ‘type testing’. The NMI performs pattern approval of several categories of instruments in Australia.

Certification to quality standards such as ISO 9001²⁸ improves the likelihood that instrument operators are properly trained and experienced, and also requires measuring instruments to be traceably calibrated.

Scientists, industrialists and business people who use approved instruments, maintain adequate quality standards and have their measuring instruments traceably calibrated by laboratories that participate in the

international framework and are accredited by NATA, are able to trust one another's measurements and don't have to take special steps to validate all measurements. For example, motor manufacturers can obtain engine components from suppliers in other countries and be confident that they will fit, and vendors and consumers can be confident that the quantities of goods purchased from retailers are correctly measured.

The aviation industry

The aviation industry has a strong and very successful emphasis on safety, and the healthcare industry, particularly anaesthesia, frequently tries to learn from aviation.³⁶ To maintain safety and the confidence of airline passengers, the Civil Aviation Authority of Australia (CASA) requires aircraft instruments to be traceably calibrated by laboratories that are accredited by NATA.³⁷

Quality management in physical measurements in medicine

In Australia all medical devices have to be registered with the Therapeutic Goods Administration (TGA). Assessment of quality and fitness for purpose of medical instruments (type-testing or pattern approval, called Declaration of Conformity by the TGA) is the responsibility of the manufacturer or 'sponsor' and evidence of this evaluation is submitted to the TGA for approval. Once an instrument is registered, however, no further formal management of the performance of medical instruments is required. For example, low cost aneroid sphygmomanometers, which are well known to be unreliable²⁰, can be used for decades without ever being checked or calibrated. Manufacturers are required to report adverse events involving all medical devices to the TGA, but erroneous measurements, if detected, do not appear to constitute adverse events.

The international standard ISO 13485 2003 *Medical devices - Quality management systems — Requirements for regulatory purposes*³⁸ (AS ISO 13485 2003 in Australia) 'specifies requirements for a quality management system that can be used by an organisation for the ... servicing of medical devices'. However, this standard does not require medical devices serviced by the organisation to be traceably calibrated. Further, the TGA does not require all medical equipment manufacturers, importers or local agents to comply with ISO 13485; conformity with the medical device regulations³⁹ can be demonstrated by other means.⁴⁰ The Australian and New Zealand standard AS/NZ 3551 2004 *Technical management programs for medical devices*⁴¹ requires test equipment used during maintenance of medical devices to be traceably calibrated, but does not require medical devices with a measuring function to be traceably calibrated. There is no regulation or law requiring commercial companies, health care institutions or clinicians to comply with AS/NZ 3551. In Australia and other countries there is no legislated or regulated requirement for medical devices that perform measurement functions to be properly maintained, regularly checked and traceably calibrated while in use. Local and international guidelines and protocols for physical measurements^{13 42-52} are written predominantly by clinicians and contain little emphasis on metrological quality control and traceability.

Audiometry is possibly the only physical medical measurement for which there is accredited calibration laboratory support for quality control in Australia (four Australian laboratories are NATA-accredited to calibrate audiometers), possibly because of occupational health and safety concerns of hearing loss in workers by unions.

Evidence of inadequate quality control of physical medical measurements

While it is well known that errors occur in a wide variety of medical measurements, caused by inadequate quality control of medical devices, there are no studies of the contribution of inadequate quality control of medical measurements to rates of misdiagnosis and other medical errors. This section briefly reviews recent reports of errors in some physical measurements and evidence of inadequate quality control.

There is an increasing trend to transfer much of the diagnosis of disease and monitoring of treatment of patients from the clinician to medical devices.⁵³ Although medical devices, particularly those that perform measurement functions, are becoming more safety-critical in healthcare,⁵³ and technical complications are the third largest category of adverse events, accounting for 13% of adverse events,⁵⁴ 'technology is seldom the focal point of investigation as a source of medical error or adverse event'.⁵⁴ Apart from the effects of errors in BP measurements on the detection of hypertension^{8 9} discussed above, the effects of inadequate quality control and systematic errors in physical medical measurements have not been studied adequately.

Investigations of medical errors usually concentrate on human error and very seldom consider medical devices.⁵³ It is possible that the under-reporting of medical device-related errors is even greater than that of other medical errors.⁵³

Questions in the Australian Senate

In 2003 the Minister for Health and Aging in the Australian Senate was questioned by Senator Lyn Allison concerning the termination of work by the National Measurement Laboratory (now the National Measurement Institute (NMI)) in ‘the important area of medical metrology’, ‘given the development of new devices and apparent lack of standards for such devices’.⁵⁵ The reply contained the following text: ‘The CSIRO has advised that the National Measurement Laboratory has engaged a scientist on a part time basis over the past 18 months to investigate the needs and opportunities for metrology and measurement traceability in medicine. Further investigation of the needs in this field has been deferred pending the establishment of the new National Measurement Institute in July 2004’. Although the NMI website states that ‘The quality, safety and performance of everything — from cars, to medical equipment, to our food and drinking water — is currently tested and regulated by NMI’,⁵⁶ as of August 2010 the NMI supports no research, development or service activity in physical medical metrology.

Blood pressure

Hypertension is the most commonly managed problem in general practice, accounting for 10% of encounters²⁵ and 7.9% of prescriptions,⁵⁷ but just under half the cases in Australia are untreated.⁵⁷ Frequent consequences of hypertension are stroke and cardiovascular disease which caused 38% of all deaths in Australia in 2002.⁵⁸ Hypertension in its early stages can be diagnosed only by measurement of blood pressure (BP). Many studies have shown that the quality control of sphygmomanometers in clinical use in Australia and other countries is inadequate,¹⁴⁻²² causing substantial over- and under-detection of hypertension.^{8,9} While clinically significant errors in BP measurements certainly occur often, they are seldom detected and never reported as medical errors. At present in Australia there is nothing to prevent clinicians from using low-cost aneroid sphygmomanometers for decades without calibration. In Germany sphygmomanometers are required to be calibrated every two years by an accredited institution.⁵⁹

Automatic sphygmomanometers use proprietary software to detect systolic and diastolic blood pressures as the cuff deflates on the upper arm or wrist. There is wide inter-device variability in automatic sphygmomanometers, therefore these devices usually undergo validation procedures using humans as transfer standards and manual blood pressure measurements as reference before they are accepted for clinical use.^{13, 51, 52} At present sphygmomanometer validations performed by any laboratory or research group are accepted by clinicians provided they are published in a peer-reviewed journal. A recent article⁶⁰ reviewed the severe weaknesses of this approach and suggested that laboratories that perform sphygmomanometer validations should be accredited to ISO 17025.²⁷ At present there is one such accredited laboratory (worldwide) at Guy’s & St Thomas’s Hospital in London, UK.

There is strong evidence that systematic errors permitted by present manual sphygmomanometer standards¹¹⁻¹³ are excessive and that standards should be tightened,^{8,10} but more evidence is needed to convince clinicians, manufacturers and the committees that write the standards. While there are a number of NATA-accredited calibration laboratories in Australia that can calibrate pressure indicators traceably over the appropriate pressure range, costs are high and few, if any, labs are capable of dealing with mercury manometers. At present no laboratories in Australia are accredited to assess other important performance characteristics of sphygmomanometers, such as presence of leaks and dynamic response.¹¹ The May 2010 draft of the sphygmomanometer standard *Non-invasive Non-automated Sphygmomanometers* published by the International Organization of Legal Metrology (OIML)⁶¹ recommends in section 7.2 that ‘Each instrument of an approved type of sphygmomanometer shall be verified periodically in accordance with applicable metrological laws and regulations of a member state or after repair.’ In Australia at the time of writing no law or regulation requires periodic verification of sphygmomanometers.

Intraocular pressure

Intraocular pressure is measured by optometrists every time a person has an eye test, and by ophthalmologists to screen for, diagnose, treat and monitor diseases such as glaucoma. Both Goldman applanation and non-contact tonometers for measuring intraocular pressure are known to produce systematic

errors if inadequately calibrated,⁶²⁻⁷⁵ and current calibration intervals may be too long.^{62 63 65 66 70 71 74} However, the effects of those errors on over- and under-detection and treatment of diseases such as glaucoma are not known and have not been studied. Goldman applanation tonometers can be checked by users using a standard weight, but these checks are not subject to metrological quality control. Full calibration of Goldman applanation tonometers requires a capability of measuring a horizontal force from zero to 50 mN with an uncertainty of approximately 0.1 mN.⁷⁶ This capability does not exist in Australia. Goldman applanation tonometers are now available with digital displays. The electronic force or torque transducers and electronics necessary to produce a digital readout are an additional concern regarding calibration. There is no traceable metrological support for calibration of applanation tonometers. Anecdotal evidence is that some ophthalmologists replace their Goldman tonometers regularly, rather than having them calibrated overseas. Equipment for calibration of non-contact tonometers is in regular use in Germany where tonometers are required to be traceably calibrated every two years,⁷⁷⁻⁷⁹ but is not readily available in Australia.

Spirometry

Spirometry is the most commonly performed pulmonary function test and is the most important method for screening for, diagnosing and monitoring respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD).⁸⁰ Spirometers incorporate flow or volume transducers to measure flow and volume of forced expiration and inspiration of maximal breaths. It is well known that the calibration of spirometers may not be stable⁸¹ and misclassification of respiratory disease does result from systematic errors in spirometer measurements,⁸² but the sensitivity of diagnoses to systematic errors is not known. A decade or two ago spirometry was done predominantly in large, hospital-based pulmonary function laboratories where technical support is usually available, but the increasing availability of low-cost portable spirometers is facilitating an increasing trend for spirometry to be performed in physicians' and GPs' offices and pharmacies where there is little or no technical support.^{80 83-87} Diseases such as COPD are diagnosed by comparison of spirometry results with absolute thresholds⁸⁸ and case finding may be performed by practice nurses,⁸⁹ therefore it is important that absolute errors in spirometry results are well controlled. The tendency for clinicians to emphasise human error over absence of quality control of equipment is also evident in spirometry.⁹⁰

The American Thoracic Society (ATS) recommends that spirometers be calibrated with syringes,⁴⁴ and suggests that volume checks of spirometers should indicate errors less than 3.5%. Calibration by syringe, however, verifies only calculated or measured overall volume that passes through the spirometer, and neglects dynamic performance. A forced expiration is a transient event with very a rapid increase in flow, and two studies suggest that even when volume calibrations meet ATS criteria, inadequate dynamic response in flow or volume meters may cause measurements of forced expiratory manoeuvres to be inaccurate.^{91 92} Munnik and colleagues also showed that between and within manufacturers, significant differences can exist between pneumotachographs.⁹² McCormack and colleagues⁹³ suggest that 3.5% error in calibration volume is too large and the upper limit should be 2%.

Spirometers that measure volume have to be corrected for the temperature (and humidity which is usually assumed to 100% RH) of the collected gas. Erroneous temperature measurements have been shown to be a cause of systematic errors in volume spirometers.⁹⁴

In a study of long-term variability in lung function measurements, Jensen and colleagues found that instrumentation accounted for up to 58% of the total variation in FEV1 (volume expired in one second).⁹⁵ Kunzli and colleagues⁹⁶ assessed the longitudinal validity of lung function measurements by testing healthy volunteers with eight spirometers that all complied with ATS standards and were calibrated according to ATS guidelines. They found systematic differences between spirometers of up to 11.3% and strongly recommended the use of the same spirometers in follow-up studies.⁹⁶

Jensen and colleagues assessed instrument accuracy and reproducibility in five commercially available laboratory pulmonary function instruments using a waveform generator.⁹⁷ Errors up to 30% in mean forced expiratory flow between 25 and 75% of expired volume were reported.

Several studies have compared portable spirometers with laboratory spirometers and found systematic differences. Bastian Lee and colleagues⁹⁸ compared the performance of a low cost paediatric spirometer intended for home use with a laboratory spirometer and found that the home spirometer over-estimated peak

expiratory flow (PEF) by approximately 55 L/min ($P < 0.05$) (up to 50% of PEF) and under-estimated forced expired volume in one second (FEV_1) by approximately 150 mL ($P < 0.05$) (up to 15% of FEV_1). In a similar study, Korhonen and colleagues⁹⁹ found that FEV_1 results are not interchangeable between a hand-held paediatric turbine spirometer and a laboratory spirometer. Viegi and colleagues found differences as large as 18% in both FEV_1 and forced vital capacity (FVC) between a portable turbine spirometer and laboratory spirometers in 14 centres.¹⁰⁰

Lum and colleagues recommend that variations between respiratory measurements in infants obtained with different instruments are so large that equipment-specific reference values are needed.¹⁰¹ Systematic measurement errors may have contributed to the disagreement in asthma diagnoses reported by Aaron and colleagues.¹⁰²

The Thoracic Society Of Australia & New Zealand (TSANZ) undertakes accreditation of pulmonary function laboratories¹⁰³ and recommends that pulmonary function testing equipment be calibrated regularly, but makes no mention of traceability and metrological quality control.¹⁰³

It is clear that spirometry results cannot be assumed to be interchangeable between laboratories or between laboratory and home measurements. Good metrological quality control should reduce the variability between instruments substantially.

Whole body plethysmography

Plethysmography is the measurement of changes in volume of a body or an organ. Whole body plethysmography uses small changes in pressure in the plethysmograph during various respiratory manoeuvres, and the ideal gas laws, to measure total thoracic gas volume and airway resistance. Difficulties that have to be overcome in whole body plethysmography are, for example, changes in gas temperature in the plethysmograph due to the presence of a warm human body, and changes in barometric pressure. The thermal time constant of the plethysmograph, which affects its volume-pressure relationship, is influenced by the presence of a subject in the fixed volume. At present, although it is possible to calibrate the flow and pressure transducers of plethysmographs, there is no method for calibrating the airway resistance measurement capability of plethysmographs.¹⁰⁴ Poorisrisak and colleagues¹⁰⁴ used biological controls to study airway resistance measured by whole body plethysmographs from the same manufacturer in six centres and found statistically and clinically significant differences between centres. The six plethysmographs used four different software versions, and a software error was found in one instrument and corrected.¹⁰⁴ Three centres that used the same software version yielded very similar airway resistances, but differences of up to 15% between instruments with different software versions remained unexplained. The authors, supported by an accompanying editorial,¹⁰⁵ identified a need for specialised equipment for calibrating plethysmographs. Whole body plethysmographs are in routine clinical use in almost every lung function laboratory in Australia, but it is unlikely that measurements are interchangeable between laboratories.

Transfer factor (diffusing capacity) for carbon monoxide (D_LCO)

The rate at which carbon monoxide (CO) diffuses from the lungs into pulmonary capillary blood is an indication of surface area and integrity of the gas-blood interface in the lungs. CO is used as indicator gas because it is strongly absorbed by haemoglobin, resulting in very low partial pressures in pulmonary blood. D_LCO is an important test in the diagnosis, treatment and monitoring of diseases such as interstitial lung disease, emphysema and COPD in which the surface for diffusion is reduced in area or impaired.¹⁰⁶ In this test the patient takes a deep breath of air containing approximately 0.3% CO and 5% helium (He) and holds the breath for approximately 10 s. CO and He in expired breath are analysed and the transfer factor calculated.

D_LCO measurements are known to have high intra- and inter-laboratory variability.^{97 107} Lack of standards and traceable calibration of medical instruments occasionally lead to a need for individual clinicians and laboratories to make extraordinary arrangements to facilitate the quality control necessary for multi-centred comparison of measurements. For example, in a multi-centred trial of inhaled insulin as a replacement for injected insulin for diabetics the surface area available in the lungs for absorption of inhaled insulin is important and was estimated in participants by D_LCO measurements.¹⁰⁸ A separate project was devised and run to standardise the measurements and set up calibration and routine checking procedures.^{107 109} The

quality control efforts of Wise, Jensen, and colleagues were praised in an editorial by Farre,¹¹⁰ but criticised by Madsen for lack of traceability of calibrations and reference materials.¹¹¹ Madsen further commented: '*I hope that this type of positive industry-driven quality control*' (i.e. metrological traceability) '*will spread from industry to our clinical work*'.¹¹¹

Quality control of gas analysers in lung function laboratories has decreased over the last few decades.¹¹² It is very likely that if the same level of standardization and quality control were practised routinely in clinical measurements as presently exists in science, industry and trade, the work of Wise, Jensen and colleagues would not have been necessary to support the inhaled insulin study.

In another study of long-term variability in lung function measurements, Jensen and colleagues found that instrumentation accounted for up to 70% of the variability in carbon monoxide diffusion observed in human subjects.⁹⁵

From the above example, it could be argued that some aspects of quality control in respiratory measurements are at a similar state of advancement as industrial and trade measurements were prior to 1875, when users had to make their own arrangements to ensure that measurements from different instruments could be compared and trusted.

Pulse oximetry

Pulse oximeters measure the oxygen saturation of haemoglobin by analysing the pulsatile attenuation of red and infrared light in arterioles in tissue. Because of the complexities of light propagation in tissue, it is difficult to calibrate pulse oximeters in-vitro, so they are usually calibrated against bench-top haemoximeters using human volunteers as transfer standards.¹¹³ Significant measurement errors have been demonstrated in manufacturer-maintained and calibrated bench-top haemoximeters, particularly at low saturations.¹¹⁴ In Australia, however, haemoximeters are usually overseen by accredited medical testing laboratories and inter-laboratory comparisons should be performed regularly, so quality control should be better than reported by Gehring and colleagues.¹¹⁴ Pulse oximeters, however are not usually maintained by medical testing laboratories and in Australia suffer from the same lack of regulatory control as other physical measurements. Bohning and colleagues¹¹⁵ studied the performance of pulse oximeters for use in sleep laboratories and found that the dynamic response of the instruments, mainly determined by internal signal processing, significantly affected (by up to 40%) their ability to detect desaturation during sleep. Van de Louw and colleagues reported that pulse oximeters perform rather poorly in intensive care units and 'high SpO₂ thresholds were necessary to detect significant hypoxemia with good sensitivity'.¹¹⁶ Wilson and colleagues reported that pulse oximeters overestimate arterial saturation to a clinically significant extent, particularly at low saturations where accurate measurements are important.¹¹⁷ Pulse oximeters are used in Australia in every operating theatre, emergency department, intensive care unit and in some ambulances and dental surgeries.

Intermittent breathing of hypoxic gas mixtures by athletes to improve performance is increasing in popularity.^{118 119} Commercial systems (called 'Hypoxicators') for producing hypoxic gas mixtures are available from suppliers in Australia (<http://www.go2altitude.com/>).¹²⁰ Pulse oximeters are used to monitor the arterial oxygen saturation of the athlete and operate a cut-off if saturation falls below 70%.¹²⁰ Hypoxic gas generators are also used to evaluate patients at risk of hypobaric hypoxia during air travel.¹²¹

Considering the lack of reported traceable calibration of the oxygen analysers used in these devices, the known limitations of pulse oximeters at low saturations^{116 117} and the inadequate quality control of pulse oximeters in Australia, hypoxic gas generators may not provide adequate protection against harmful hypoxic gas mixtures.

Sleep studies

One quarter of middle-aged men and 10% of women in Australia suffer from obstructive sleep apnoea (OSA).¹²² OSA is associated with hypertension (both systemic and pulmonary), cardiovascular disease, respiratory failure, diabetes, cognitive dysfunction¹²³ and motor vehicle and occupational accidents.¹²⁴ OSA is diagnosed by 8 hour sleep studies during which a number of continuous measurements are made: electrical activity of the brain (EEG), heart (ECG), eye (EOG) and the muscles that control swallowing, respiratory air flow, movements of thorax and abdomen related to respiration, and arterial oxygen saturation. Respiratory flow is recorded qualitatively using a thermistor or pressure changes induced in nasal prongs.

While some of the measurements are qualitative, EEG, ECG and arterial oxygen saturation by pulse oximetry are quantitative — both amplitude and frequency content are important for diagnosis. Campbell describes the calibration of EEG instruments used for sleep research, but does not discuss quality control of the reference instruments used in calibration.¹²⁵ Guidelines published by the Australasian Sleep Association advise regular calibration of equipment but do not discuss traceability and metrological quality control.^{126 127}

There are many private and public sleep laboratories in Australia. Medicare funded or co-funded 82,000 diagnostic sleep studies in Australia at a cost of \$ 54.5 million in the 2009-2010 financial year.²⁴

Electrocardiograph (ECG)

Both amplitude and phase response of ECG equipment may affect the ECG trace, leading to incorrect interpretation. Recognition of artefact on the ECG is poor among physicians.¹²⁸ Inappropriate filter settings or incorrectly designed filters¹²⁹⁻¹³³ or incorrect design or failure of electronic components in the signal processing path may alter the shape of the ECG trace and cause incorrect diagnoses.^{134 135} Electronic components, the interconnections between components provided by printed circuit boards and connecting cables, and mechanical components¹³⁶ may malfunction and alter filter, amplifier or display characteristics and hence alter the ECG trace. Failures or design flaws that cause subtle changes, as reported by Tyler and colleagues,^{134 135} may not be detected by non-technical users. Regular traceable calibration and safety checks by technically competent people of both amplitude and phase characteristics are essential to ensure accurate ECG interpretation.

Measurement of paediatric drug dose

Tadros and colleagues found that cups to measure paediatric liquid medication doses (2.5 and 5 mL), commonly sold with over-the-counter medications, are often marked incorrectly and delivered volumes an average of 0.63 mL too high.¹³⁷ The maximum error was 1.15 mL. Uppal and colleagues found that many oral and intravenous drugs require volumes of less than 0.1 mL to be prepared for children and infants, and devices are not available for measuring these volumes with adequate accuracy.¹³⁸

New and emerging measurements for which quality control infrastructure is inadequate

Forced oscillation technique (FOT) for measurement of airway mechanics

In the forced oscillation technique, first reported in 1968,¹³⁹ a low-amplitude sinusoidal pressure is applied at the mouth at frequencies usually between 4 and 30 Hz, and pressure and flow are measured. The vector ratio of pressure to flow gives the impedance of the airway in amplitude and phase (or resistance and reactance) as a function of frequency. The excitation amplitude is low (< 3 hPa peak-peak)⁵⁰ to minimise non-linear effects. FOT instruments have to measure small oscillatory flows and pressures superimposed on tidal breathing. Flow transducers are usually resistance pneumotachographs that generate a small differential pressure proportional to flow. During measurements, airway pressure oscillates at the same frequency as flow, but at an amplitude substantially greater than the differential pressure generated by the pneumotachograph, therefore the common mode rejection capability of the differential pressure transducer is critical to the correct operation of FOT instruments.¹⁴⁰ Measurement of common mode rejection ratio of differential pressure transducers requires specialised equipment and careful technique.^{141 142} Separate calibration of flow and pressure measurement systems is not sufficient for accurate measurement, and calibration of the entire FOT measurement system with known impedances is necessary.⁵⁰ Reference impedances with well known or calculable values are not readily available and are difficult to construct. The mechanics of the lungs are known to be non-linear,^{50 143 144} and most FOT instruments measure respiratory impedance at three or more frequencies simultaneously^{145 146} but the possibility of interference by harmonics and intermodulation distortion products has not been properly investigated.

At present FOT is used for research in asthma,¹⁴⁷⁻¹⁴⁹ COPD,^{146 147} cystic fibrosis,¹⁵⁰ upper airway pathology¹⁵¹ and other respiratory and airway diseases in children and adults in ambulatory and intensive care¹⁵² settings and in sleep laboratories.^{153 154} FOT is starting to be used in clinical settings,^{50 150 155} but wide acceptance for routine clinical investigations is unlikely to occur until standards for the instruments, calibration infrastructure and widely accepted reference values of respiratory impedance are available.

Studies of respiratory impedance are performed with uncalibrated instruments and no quality control¹⁵⁶ and report results that differ from previous studies of similar subjects.¹⁵⁶ Some research groups are currently evaluating FOT for home monitoring of respiratory mechanics.¹⁵⁷ FOT is in routine use in research laboratories in Australia in Adelaide,¹⁵⁸ Perth,¹⁵⁹ Sydney,¹⁶⁰ Melbourne¹⁶¹ and Brisbane.¹⁶² Quality control of FOT and other respiratory instruments is particularly important when normal or reference values are determined.¹⁴⁵

Multiple breath insoluble gas washout (MBIGW)

Adult lungs are typically around 3 L in volume, containing airways that branch 23 times and terminate in approximately 8 million alveoli. Tidal volume is approximately 0.5 L, therefore only a small fraction of gas in the lungs is exchanged at each breath. Ideally gas turnover in all alveoli is identical, but disease and age can cause ventilation to be distributed unevenly. In multiple breath insoluble gas washout, an indicator gas that has a low solubility in blood and tissue is washed out of the lungs over several minutes, and the decline in indicator concentration in expired gas is analysed to quantify heterogeneity in ventilation. Commonly used indicator gases are sulphur hexafluoride (SF₆) and nitrogen (N₂). In healthy lungs the washout closely follows a single exponential curve with a single time constant, while in diseased lungs the washout is prolonged when parts of the lungs are poorly ventilated. MBIGW is particularly sensitive to dysfunction of the small airways in the lungs¹⁶³ and is used for investigating asthma,¹⁶⁴ COPD,^{165 166} cystic fibrosis^{150 163 167} and respiratory disease in neonates.^{168 169}

Gas flow and indicator concentration at the mouth are measured continuously during a washout. The analysis requires synchronised data, therefore the differences in dynamic responses of the flow measurement system and gas analyser have to be small to avoid systematic errors.¹⁷⁰ Most gas analysers are non-linear and have significant delay, and many have long rise times. Some are sensitive to water vapour in expired gas. At present there is no generally accepted method for linearising the gas analyser response and matching the dynamic responses of the two measurement systems, and investigators often 'estimate' corrections.¹⁶⁷ Corrections for changes in gas temperature and humidity are usually necessary to avoid systematic errors in flow and volume measurements, but some instruments neglect this correction.¹⁷¹ The more sophisticated indices of lung function calculated from insoluble gas washouts, involving effective double differentiation of gas concentration with respect to expired volume,^{164 172} are probably more sensitive to non-linearity in the gas analyser, mismatched dynamic responses and incorrect temperature and humidity correction.

MBIGW is in routine use in research laboratories in Australia in Perth,¹⁷³ Sydney,¹⁶⁴ Melbourne¹⁶⁸ and Brisbane.¹⁷⁴ Routine clinical use is proposed.^{163 175}

Pulse wave velocity, arterial stiffness and pulse waveform analysis

Cardiovascular disease accounted for 34% of all deaths in Australia in 2006.¹⁷⁶ At present the most commonly used methods for estimating risk of cardiovascular disease use equations derived from the Framingham study.¹⁷⁷ The independent variables in these equations are gender, age, blood pressure, cholesterol levels, smoking habit, presence of diabetes and presence of left ventricular hypertrophy. Recently a number of new independent, predictor variables have been reported to contribute to estimates of cardiovascular risk and mortality. These variables include the velocity at which pulse waves propagate through large arteries, which is related to arterial stiffness,^{178 179} and augmentation index, an index derived from the pressure waveform in the ascending aorta.¹⁸⁰ The ascending aortic pressure waveform is estimated non-invasively using a generalised transfer function that is assumed to be valid for all patients.¹⁷⁹ Independent variables in the transfer function are systolic and diastolic blood pressures measured conventionally using a cuff on the upper arm, and a pressure waveform measured non-invasively in the radial artery at the wrist by applanation tonometry.¹⁷⁹ Two commercially available instruments give substantially different values for pulse wave velocity.^{181 182} Kips and colleagues found a mean difference of 18.8 mm Hg between central systolic BP estimates made by Sphygmocor and Omron HEM-9000AI instruments, which they concluded was caused by algorithm differences.¹⁸³ At present there is no accredited metrological support for quality control of these measurements.

Telemedcare

The TeleMedCare Health Monitor¹⁸⁴ is a multifunction monitor designed and manufactured by an Australian company for use in the home, in nursing homes and in primary care and community health settings. It

measures and records body weight, temperature, non-invasive BP, arterial oxygen saturation by pulse oximetry, blood glucose, spirometry and electrocardiogram. It is capable of network communication, video conferencing and scheduling. There is, however, no evidence on the manufacturer's website of any metrological quality control of the measurements.

Disclosure of measurement errors

Improved quality control of clinical measurements will inevitably reveal medical errors that are unrecognised at present. When a measuring instrument such as sphygmomanometer or tonometer is found to be producing erroneous measurements resulting in incorrect diagnoses, it is likely that several patients will be affected. The number of patients affected will depend on the calibration interval and the rate at which patients were exposed to the device after its last successful calibration. Hence clinicians will need to develop procedures for identifying and informing multiple patients of the errors and taking corrective action.¹⁸⁵

Other countries

Countries that have formal, regular metrological control over physical clinical measurements include:

- Germany (sphygmomanometers⁵⁹ and tonometers⁷⁸),
- Brazil (clinical thermometers, sphygmomanometers),¹⁸⁶
- Lithuania (audiometers, clinical thermometers, sphygmomanometers, tonometers, ergometers, medical weighing instruments),¹⁸⁷
- Latvia (sphygmomanometers)¹⁸⁷
- Czech Republic (clinical thermometers, sphygmomanometers, tonometers)¹⁸⁷
- Switzerland (audiometers, sphygmomanometers)¹⁸⁷
- Taiwan (sphygmomanometers).¹⁸⁸

Conclusions

Metrological quality control of physical measurements in medicine in Australia lags well behind the quality control of other measurements that are important to society. There is a clear, unmet need in Australia and other countries to link physical medical measurements to the international traceability framework to lift quality to the standards that pertain to medical laboratory measurements and other measurements such as those in science, industry and trade. The health care system, however, is very sensitive to increasing costs. There is therefore a need for further multidisciplinary research to investigate and quantify the impacts of systematic errors in clinical measurements and estimate the costs and benefits of integrating clinical measurements with the international measurement framework. This research should inform the incorporation of sound metrological principles in clinical guidelines, standards and regulations that cover clinical measurements, and guide the development of the infrastructure necessary to provide appropriate quality control. Many of the physical clinical measurements discussed in this report are important in monitoring chronic diseases (e.g. hypertension, asthma, COPD, glaucoma) in older people. Therefore quality control of measurements will become increasingly important as the population ages. Quality control may increase costs of measurements but reduction in systematic errors and inter-device variability will improve detection, treatment and follow-up of disease and hence reduce overall health care costs and improve outcomes.

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